

# Protocol

This trial protocol has been provided by the authors to give readers additional information about their work.

Protocol for: Wilt TJ, Brawer MK, Jones KM, et al. Radical prostatectomy versus observation for localized prostate cancer. *N Engl J Med* 2012;367:203-13. DOI: 10.1056/NEJMoa1113162

May 9, 2012

Re: 11-13162.R3 - Radical Prostatectomy Versus Observation for Localized Prostate Cancer

"This supplement contains the following items:

1. Original protocol, final protocol, summary of changes.
2. Original statistical analysis plan, final statistical analysis plan, summary of changes"

Sincerely and thank you,

A handwritten signature in black ink, appearing to read "Timothy J. Wilt". The signature is fluid and cursive, with the first name "Timothy" and last name "Wilt" clearly legible.

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**VA COOPERATIVE STUDY 407**

**"PROSTATE CANCER INTERVENTION VERSUS OBSERVATION TRIAL (PIVOT):  
A RANDOMIZED TRIAL COMPARING RADICAL PROSTATECTOMY VERSUS  
PALLIATIVE EXPECTANT MANAGEMENT FOR THE TREATMENT OF  
CLINICALLY LOCALIZED PROSTATE CANCER"**

**PLANNING COMMITTEE**

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Michael K. Brawer, M.D., Chief, Section of Urology, Seattle VAMC (Co-Chairman)

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**- PRIVILEGED AND CONFIDENTIAL -**

Not to be Disseminated Beyond its Official

Committee Function and Use

REVISED OCTOBER, 1994

# **CS 407 "PIVOT" RESTRUCTURED STUDY BUDGET**

**EFFECTIVE OCTOBER 1, 1999**

***RECRUITMENT PERIOD WILL END ON NOVEMBER 30,2001  
FOLLOW-UP PERIOD WILL END NOVEMBER 30, 2009***

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## **FUNDING FOR ALL CENTERS- PAID QUARTERLY**

- \$200 per month for screening log based on "Monthly PIVOT Screening Payment form" submitted to Perry Point
- \$3,500 per patient randomized
- \$500 follow-up per patient/year based on submitted "Clinic Visit Follow-up" Form 04
- \$75 per completed and submitted PIVOT subprotocol survey, "Treatment Preferences and Health Outcomes in Men with Clinically Localized Prostate Cancer".

## **ADDITIONAL INCENTIVES**

- \$5,000 lump sum for randomizing 4-7 patients between October 1, 1999 thru September 30,2000 or between October 1, 2000 thru September 30,2001.
- \$10,000 lump sum for randomizing 8-11 patients between October 1, 1999 thru September 30,2000 or between October 1, 2000 thru September 30,2001.
- \$15,000 lump sum for randomizing 12 or more patients between October 1, 1999 thru September 30,2000 or between October 1, 2000 thru September 30,2001.

*The following protocol changes are effective immediately. Please insert this page in your PIVOT Manual of Operations, and remind your coordinators and colleagues of these changes.*

- Mandatory bone scans are reduced from an annual basis to baseline, year five, ten, and fifteen.
- Hormonal therapy in the expectant management group is left to the discretion of the investigator. The type of hormonal therapy and reason for such use will be recorded on Study Form 05. To minimize treatment related side effects, physicians are encouraged to reserve hormone therapy for symptomatic disease or if there is evidence of cancer progression. However, hormone therapy use is at the investigator's discretion. This may be utilized to help avoid crossovers to surgery or radiation.
- PSA specimens will be unblinded in the expectant management group and provided to patients and investigators if the PSA level exceeds 20. Patients enrolled in the study with a baseline PSA greater than 20 will not be blinded to their PSA.
- The window of eligibility for enrollment in the trial from the time of diagnosis of CAP is extended to 12 months.

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*You should notify your local institutional review board and provide them with a copy of the enclosed protocol changes. Such changes should be routinely processed through expedited review and should not delay or halt ongoing screening and recruitment.*

**These changes, in addition to enhancing patient safety, will reduce costs and streamline the operations of the study. They will enhance recruitment and make the results more applicable to the current practice setting for patients with clinically localized prostate cancer.**

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DEPARTMENT OF VETERANS AFFAIRS  
Medical Center  
Perry Point MD 21902

August 5, 1993

In Reply Refer To: 641/151E  
CSP #93/407

Daniel Deykin, M.D.  
Chief, Cooperative Studies Program (151-I)  
VA Medical Center  
150 South Huntington Avenue  
Boston, MA 02130

Dear Dr. Deykin:

The Planning Committee and I agree that VA Cooperative Study #407, "Prostate Cancer Intervention Versus Observation Trial (PIVOT): A Randomized Trial Comparing Radical Prostatectomy Versus Palliative Expectant Management for the Treatment of Clinically Localized Prostate Cancer," is ready for submission to the Cooperative Studies Evaluation Committee. There are a few issues that I feel need to be brought to the attention of CSEC. Most of these issues are related in some way to the funding of the study. The first issue that I feel that CSEC should be aware of is the fact that the study will be jointly funded by the VA and the National Cancer Institute (NCI). Although the study was originally proposed as a VA cooperative study, the large number of centers required (80) made it necessary to seek non-VA centers and support. Thus, the Principal Proponent's have approached NCI about a collaboration. Since neither the VA nor NCI would be able to do the study by themselves, a joint effort is being proposed. The VA intends to identify 45 participating centers with NCI identifying 30-40 centers.

The current agreement with NCI is that the VA will fund the VA centers and that NCI will fund the non-VA centers. Data management and statistical support would be provided by the Perry Point CSPCC. Other support for the study, such as the Chairman's Office and the study's central PSA laboratory, is currently in the VA budget. However, as the letter of support from the NCI Project Office (see Appendix D) indicates, there is a possibility that NCI will make additional funds available for the study. This will have to be worked out in the upcoming months.

The second issue that I feel needs to be brought to the attention of CSEC is how the VA participating centers will be funded. Unlike the vast majority of VA cooperative studies that place a study assistant at each participating center, in this study, investigators will be given funds based on the amount of work that they do. They will be given \$1,000 for each patient randomized, \$400 to \$500 for each patient in follow-up each year, \$50 for each patient who watches the study's videotape, and \$150 for each monthly patient screening log that they complete. This model of funding has been successfully applied in the DIG Study (CS #995, "Trial to Evaluate the Effect of Digitalis on Mortality in Heart Failure [VA-NHLBI])" that is coordinated at the Perry Point CSPCC. I believe that this funding model can also be successfully applied to this study because the study procedures and forms have been kept simple. Even with this funding model, the total cost for the VA portion of the study will be about \$15.5 million. These costs will be spread over 16 years, however. The highest costs (about \$4.2 million) will occur during the first three years when recruitment is taking place.

Daniel Deykin, M.D.

2.  
August 5, 1993

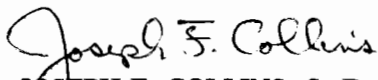
A third issue that I would like to address is the beyond core costs for the CSPCC. The CSPCC is requesting two FTE over the course of the study. We have never requested additional personnel before. We will need a Project Manager and an additional Computer Assistant. With the coordination and data management of 80 potential sites including dealings with the various NCI coordinating centers, it is essential that there be a dedicated person to handle administrative and protocol aspects of the study and one to handle the data management aspects. Having such staff has been extremely important for both the DIG Study (CS #995) and our studies with the National Institute on Drug Abuse (CS #999 studies). With our current workload, it would not be possible to use my core staff for these tasks. However, this will be monitored over the course of the study and any vacancies during the course of the study will only be filled if needed.

A fourth issue which also concerns the budget is that the cost of the PSA kits is included in the central laboratory budget. There is a good possibility that these kits will be donated by the manufacturer (Abbott). If the kits are donated, then the costs for the central laboratory will be reduced by over \$700,000.

The study itself is one that I believe is very important and very timely. There has been a push lately in prostate cancer, as well as all cancers, to develop screening tests that will enable the earliest detection possible of the cancer. On the other hand, there have been recent articles questioning the value of early intervention in prostate cancer because the cancer is slow growing for the most part and the risk of intervention may be worse than the disease if quality life expectancy is not increased. Thus, it is also a study where a valuable result is obtained no matter what the outcome. If early intervention is shown to improve quality life expectancy, then thousands of lives could be lengthened by the early detection and treatment of cancer. However, if early intervention does not improve quality life expectancy, then huge cost savings could be achieved by not providing screening and treatment for early prostate cancer and thousands of men each year will not be subjected to the risks and morbidity involved with the early treatment. The letter of support from the NCI Project Officer in Appendix D of the proposal indicates that the NCI also considers this study to be very important.


While the Co-Principal Proponents are relatively young (which is an advantage in a 16-year study), they both have been involved extensively in research and both have been investigators in other VA cooperative studies. I believe that both Proponents are highly capable and, if CSEC were to approve the study, there is a high probability that the study would be successfully completed.

Sincerely,

  
JOSEPH F. COLLINS, Sc.D.  
Chief, Cooperative Studies  
Program Coordinating Center

---

CONCUR:

  
DAVID G. WEISS, Ph.D.

## ABSTRACT

Cancer of the prostate (CAP) is the most common nondermatologic cancer and the second most frequent cause of cancer deaths in men. Cure is currently not possible for disseminated disease. Cancer confined to the prostate is believed to be curable, with the most frequently recommended therapy being surgical extirpation of the tumor with radical prostatectomy. However, despite increasing cancer detection and surgical treatment, population-based mortality rates from prostate cancer have not decreased nationally nor in states with high rates of radical prostatectomy. Existing evidence has not clearly demonstrated the therapeutic benefit of radical prostatectomy compared to expectant management in the treatment of localized prostate cancer. Data from case series, structured review of the medical literature and a decision analysis model suggest that either treatment approach provides equivalent all-cause and prostate cancer specific mortality as well as quality-adjusted life expectancy (3-8).

While radical prostatectomy provides potentially curative removal of the cancer, it subjects patients to the morbidity and mortality of surgery which may be neither necessary nor effective. Expectant management does not offer complete removal of cancer which may result in development of symptoms or metastatic progression. However, it provides palliative therapy and avoids potentially excessive and morbid interventions in asymptomatic patients.

Screening programs have been advocated to detect CAP while it is still localized in hope that cure is possible. Before early detection programs can rationally be implemented the following question must first be answered: does early treatment of clinically localized prostate cancer with radical prostatectomy reduce all-cause and prostate cancer specific mortality and morbidity compared to expectant management? The primary objective of our proposed study is to determine which of two strategies is superior for the management of clinically localized CAP: 1) radical prostatectomy with early intervention for disease persistence or recurrence or 2) expectant management with reservation of therapy for palliative treatment of symptomatic or metastatic disease progression.

- Inclusion Criteria:**
1. Age  $\leq$  75
  2. T1 or T2, NX, MO adenocarcinoma of the prostate (all histologic grades)
- Exclusion Criteria:**
1. Coexisting medical conditions expected to result in a life expectancy  $<$  10 years (e.g., severe cardiac, pulmonary, liver or renal disease)
  2. Prior therapy for prostate cancer
  3. Evidence of nonlocalized disease including:
    - a) PSA  $>$  50
    - b) Bone scan consistent with prostate cancer
    - c) Other imaging/lab studies indicating nonlocalized prostate cancer
  4. Current use of estrogens, androgen blocking drugs, or finasteride
- Patient Recruitment:** From urology, general medical, oncology or community screening clinics; CAP support groups; pathology, laboratory, ultrasound logs indicating prostate cancer or elevated PSA. Use of patient and family educational videotapes and written materials.
- Randomized Rx Arms:**
- \* Radical prostatectomy, plus intervention for evidence of disease persistence or recurrence.
  - \* Expectant management with palliative therapy reserved for symptomatic or metastatic disease progression.
- Follow-Up Visits:** Schedule of Visits: 6 weeks following randomization, every 3 months the first year and every 6 months until the end of the trial (minimum 12 years; maximum 15 years).
- Visit Protocols:** Every visit: Digital rectal examination, urologic symptoms, prostate cancer quality of life questionnaires, PSA. Annual visit: Bone scan, serologic samples for central laboratory.
- Laboratory:** Local Laboratory: Pathologic and histologic diagnosis of prostate cancer, PSA.  
Central Laboratory: Tissue specimen samples for confirmation, tissue and serum bank for special studies and PSA assays.
- End Points:** Primary: All cause mortality. Secondary: Prostate cancer specific mortality and morbidity, quality of life, cost effectiveness, morphologic, histologic, laboratory and demographic predictors of outcomes.

## I. INTRODUCTION

Cancer of the prostate (CAP) is the most common nondermatologic cancer and the second most frequent cause of cancer deaths in men (1). Cure is currently not possible for disseminated disease. Cancer confined to the prostate is believed to be curable, with the most frequently recommended therapy being surgical extirpation of the tumor with radical prostatectomy. However, despite increasing cancer detection and surgical treatment, population-based mortality rates from prostate cancer have not decreased nationally nor in states with high rates of radical prostatectomy.

Existing evidence has not clearly demonstrated the therapeutic benefit of radical prostatectomy compared to expectant management in the treatment of localized prostate cancer (2). Data from case series, structured review of the medical literature and a decision analysis model suggest that either treatment approach provides equivalent all-cause and prostate cancer specific mortality as well as quality-adjusted life expectancy (3-8). The only randomized trial was limited by small sample size and incomplete clinical staging. However, the results showed no difference between prostatectomy and expectant management (9). Recent information in the medical and lay press has resulted in an increased interest and heightened controversy regarding management of clinically localized prostate cancer (10-15).

Radical prostatectomy provides potentially curative removal of the cancer. However, radical prostatectomy subjects patients to the morbidity and mortality of the surgery and may be neither necessary nor effective. Expectant management does not offer complete removal of cancer. Patients may develop symptomatic or metastatic progression that was previously localized. However, it provides palliative therapy if there is symptomatic or metastatic disease progression. Furthermore, expectant management avoids potentially excessive and morbid interventions in asymptomatic patients, and emphasizes management approaches that focus on relieving symptoms while minimizing therapeutic complications.

Screening programs have been advocated to detect CAP while it is still localized in hope that cure is possible. Before early detection programs can rationally be implemented the following question must first be answered: does early treatment of clinically localized prostate cancer with radical

prostatectomy reduce all-cause and prostate cancer specific mortality and morbidity compared to expectant management?

The primary objective of our proposed study is to determine which of two strategies is superior for the management of clinically localized CAP: 1) radical prostatectomy with early intervention for disease persistence or recurrence or 2) expectant management with reservation of therapy for palliative treatment of symptomatic or metastatic disease progression. Outcomes will include total mortality, CAP mortality, disease free and progression free survival, morbidity and quality of life.

This objective will be achieved by conducting a randomized controlled trial in 2000 men with clinically localized prostate cancer at 45 VA Medical Centers through the VA Cooperative Studies Program and at 35 private medical centers through the National Cancer Institute.

## **II. BACKGROUND AND RATIONALE**

### **A. Epidemiology**

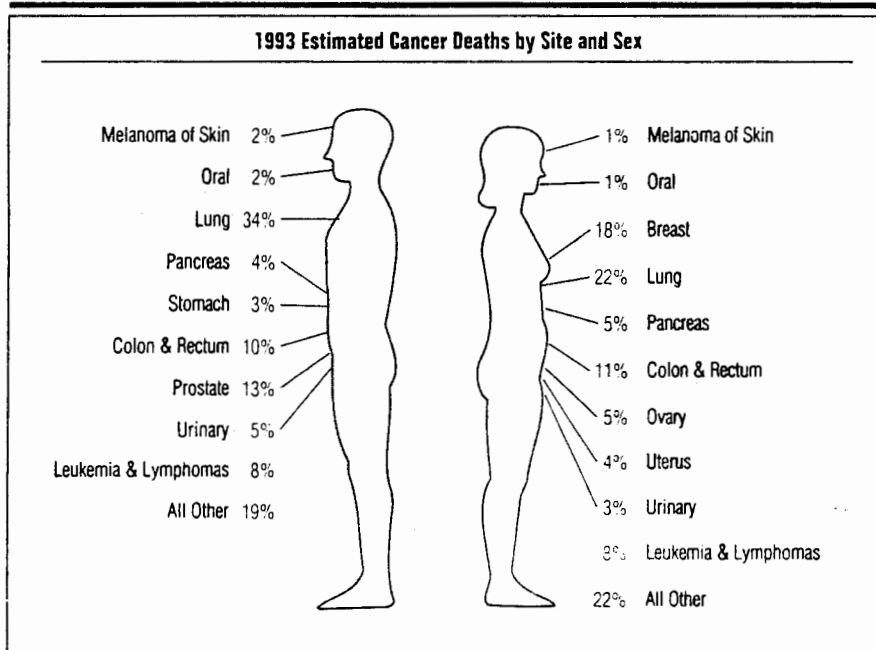
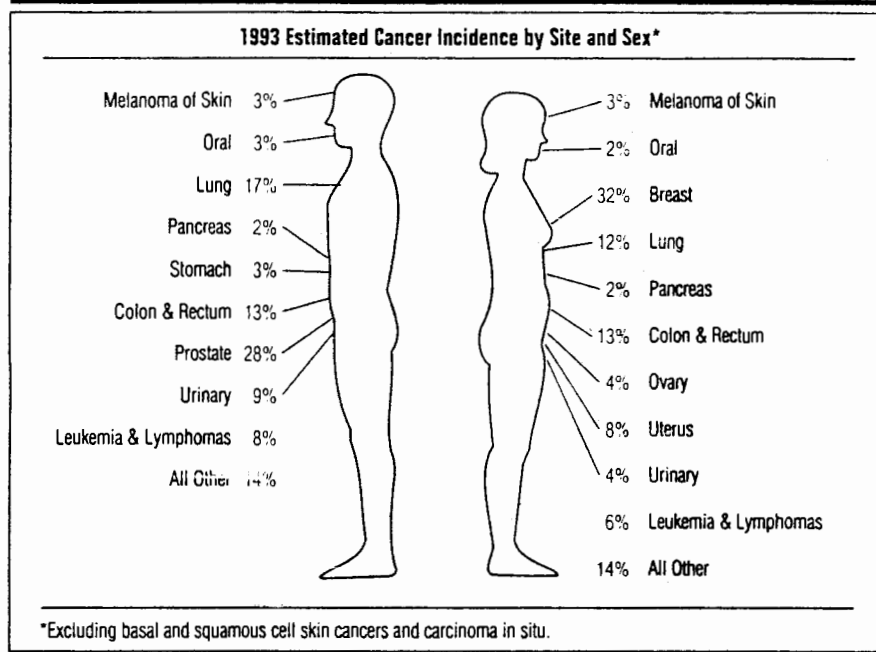
Cancer of the prostate is the most frequently diagnosed nondermatologic cancer and the second leading cause of cancer related mortality (Figure 1). In 1993 it is estimated that 165,000 cases of CAP will be diagnosed and 35,000 men will die due to prostate cancer(1). Age adjusted incidence rates of CAP have risen over the last decade for both white and black men (8% and 30% respectively). During those years, the death rates increased 7.5% in white men and 5.9% in blacks. CAP increases with age, with the risk of disease rising sharply above 50. The median age at diagnosis is 72 years. In addition to age, suspected or known risk factors for the development of prostate cancer include a family history of prostate cancer, black race, and smoking history.

Continued improvements in life expectancy and a shift in the age distribution in favor of an older population will increase the number of patients with and dying of prostate cancer. Additionally, newer early CAP detection methods used in large scale screening and case detection programs (e.g. prostate specific antigen [PSA] and transrectal ultrasound [TRUS]) will increase the number of clinically detected prostate cancers that previously remained undiagnosed. The increased detection of prostate cancer has been paralleled by an increase in the treatment modalities provided. In

FIGURE 1

1993 Estimated Cancer Incidence (Top)  
and Deaths (Bottom) by Site and Sex

CA CANCER J CLIN 1993;43:7-26



particular, the rate of radical prostatectomies has risen almost six fold from 1987-1992 (Figure 2). Despite the marked increased utilization of radical prostatectomy and radiation therapy for clinically localized prostate cancer, death from prostate cancer has not been reduced (Figure 3). This suggests that current methods utilized for early therapy of clinically localized prostate cancer may not be optimal.

Biologically, the concept of surgical cure is based on the assumption that prostate cancer does not metastasize until after it has become clinically detectable. Radical prostatectomy series indicate excellent disease free and overall survival especially in patients with clinically detectable small volume (T1) and well differentiated (Gleason 1-3) tumors. Surgery theoretically offers potential cure in these patients. However, small, well differentiated prostate cancers tend to grow slowly. Observational studies indicate that most of these patients die of causes unrelated to their prostate cancer. Therefore, early detection and subsequent surgical intervention in these individuals may result in unnecessary evaluations, anxiety, and risk.

Conversely, patients with large volume or poorly differentiated CAP have a high probability of pathologically confirmed disseminated disease or develop cancer recurrence despite apparent complete extirpation by radical prostatectomy. Therefore, while these patients have a poor 10 year survival with expectant management they also are unlikely to be cured by surgery. Even in patients with pathologically defined localized disease, CAP recurrence at 10 years has been demonstrated in up to 40% of patients having a radical prostatectomy (9, 16-22). Furthermore, 20% of these patients die from their prostate cancer despite undergoing radical prostatectomy. These patients therefore, have been exposed to the morbidity and mortality of a noncurative surgical procedure. It is possible, however, that if patients with this type of cancer were detected earlier and received prostatectomy that they may be cured of their prostate cancer.

Only one study has compared the outcomes of patients receiving radical prostatectomy with those allocated to expectant management (9). In the VACURG 2 study, there was no difference in survival at 15 years between the prostatectomy and expectant management group. The results of this study are limited by small sample size, incomplete clinical staging and uneven randomization of poorly differentiated cancers.

Figure 2 Time Trends of Radical Prostatectomy among Male Medicare Beneficiaries

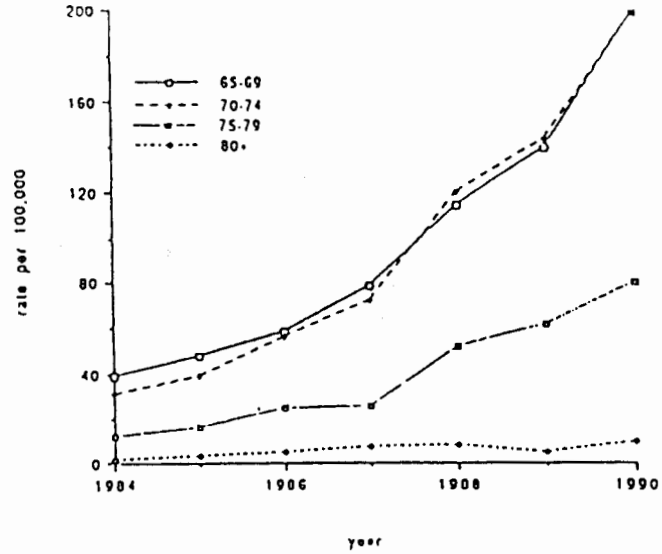
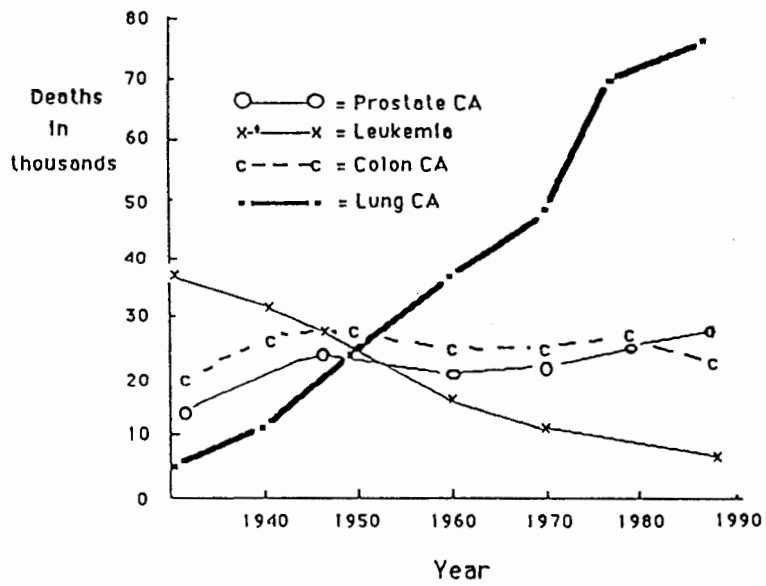


Figure 3: Age adjusted Cancer death rates (1930-1988)





## B. Natural History and Expectant Management of CAP

Because of the high prevalence of cancer in the prostate found at autopsy of men who die of other causes, the slow progression rate of the tumor, the advanced age and comorbid conditions at diagnosis, patients with CAP are said to be more likely to die *with* rather than *from* their disease. Estimates from autopsy studies indicate that 30% of men over the age of 50 have prostate cancer but that only 1 in 200 men with carcinoma of the prostate will die from their disease. Approximately 10% of men over 50 years will have progression of CAP so that it is clinically detectable or causes symptoms. In these patients, the mortality rate increases to one in four (23).

Early CAP detection and treatment programs presume that treatment with radical prostatectomy prolongs survival in subjects with clinically localized CAP. This presumption is not convincingly supported by results from observational studies, case series, structured review of the medical literature, a decision analysis model and a small clinical trial (Tables 1 and 2) (3-5, 9-22, 24). These studies demonstrate that the therapeutic approach of expectant management and palliative therapy reserved for symptomatic or metastatic disease progression provides similar 10- year survival rates and quality-adjusted life expectancy compared to radical prostatectomy.

**Table 1: Results of Five Studies of Observation for Clinically Localized CAP**

Author (Ref)	Number Patients	Follow-up Years	Overall Mortality (%)	CAP Mortality (%)	CAP Progression (% Includes CAP Death)
Johansson (3)	223	10.2	56	8	34
Whitmore (4)	75	9.5	39	15	69
Hanash (24)	179	15	55	45	NA
George (5)	120	7	44	4	83
Madsen (9)	50	10	52	6	18

Expectant management is generally recommended for clinically localized CAP in Europe. This approach is believed to provide equal long-term survival to prostatectomy and avoid operative morbidity and mortality (3-5, 9, 24). In the United States, expectant management is the treatment modality employed in 66% of Stage A and 17% of Stage B CAP patients. Morbidity due to progression

of disease has generally been successfully treated with hormone manipulation and conservative urologic procedures. Thus, prevention or treatment of symptoms from the primary tumor is not an important indication for radical prostatectomy (3).

A structured review of the medical literature revealed that the mean age of patients treated by expectant management was 71 years, 7% had poorly differentiated CAP, and the median annual all-cause and prostate cancer specific mortality rates were 0.060 (95% CI = 0.050-0.104) and 0.009 (0.006-0.012) respectively (12).

### C. Surgical Treatment of CAP

The principal basis for support of surgical treatment for CAP is the superior 10-year survival rates in individuals with localized disease compared to those with metastatic prostate cancer. The 10-year survival in patients with metastatic disease is less than 15%. In comparison, the 10-year overall and prostate cancer specific survival in patients with clinically localized CAP receiving radical prostatectomy are approximately 55% and 85% respectively (Table 2) (9, 16-22). This difference is often interpreted to mean that if prostate cancer is found "early" enough, it can be excised before it metastasizes, resulting in the patient being "cured" of an otherwise fatal disease. This interpretation does not take into account the problems of lead-time and length (or susceptibility) bias in which an apparent benefit of treatment spuriously results from preferentially selecting patients with early or indolent disease and then comparing them with others not so selected.

**Table 2: Results from Studies of Radical Prostatectomy for Localized CAP**

Author (Ref)	Number Patients	Total Mortality Rate: %		CAP Mortality %	CAP Progression: (% Includes CAP Death)
		5-Year	10-Year		
Berlin (16)	143	20	48	NA	NA
Kopecky (17)	73	27	50	NA	NA
Belt (18)	185	22	45	8	14
Belt (18)	267	35	60	19	40
Veenema (19)	159	16	48	8	NA
Correa (20)	67	8	27	5	24
Madsen (9)	61	22	57	4	15
Smith (21)	186	NA	40	22	35
Box (22)	212	18	37	NA	NA

Complication rates of surgical therapy vary with the surgeon and technique utilized. These include a perioperative mortality of (0.5-2%), urinary incontinence (0-30%), vesicourethral stricture (12%), impotence (25-95%) and rectal injury requiring colostomy (1-3%) (12).

In the structured literature review by Wasson, the average age of patients treated with radical prostatectomy was 63 years, 11% had poorly differentiated CAP, the median annual all-cause and cancer-specific death rates were 0.032 (95% CI = 0.020-0.044) and 0.052 per patient year (95% CI = 0.009-0.015) respectively (12).

**D. Radiation Treatment of CAP**

Radical prostatectomy is the most frequently recommended intervention for patients with clinically localized CAP. Radiation therapy is also believed by some to provide comparable survival to radical prostatectomy in these patients (25-27). However, comparison of radiotherapy results with those of surgery is difficult. Radiotherapy series report outcomes on the basis of clinical staging. Surgical series frequently exclude the subset of patients with clinical Stage T1 and T2 disease found to have

metastatic nodal disease or extracapsular extension during surgery. Ten-year follow-up on patients having radiotherapy for clinically localized CAP is limited but indicate an overall survival of 45%.

A VA Oncology Group cooperative trial has provided evidence that patients treated with radiation had a higher rate of disease recurrence than patients treated with prostatectomy (28). Therefore, radiation therapy is generally reserved for patients judged to be poor surgical candidates or to have disease extending beyond the prostate gland (25-27). A prospective randomized trial, Southwest Oncology Group [SWOG #8890], was initiated comparing external beam irradiation with radical prostatectomy for clinical Stage A and B disease (29). This trial was discontinued because of low patient recruitment. Complications from radiation are similar to prostatectomy and include incontinence, impotence and rectal injury requiring colostomy.

The structured literature review of Wasson indicates that the mean age of patients treated with radiation therapy is 66 years, 21% have poorly differentiated CAP, and the median annual all-cause and prostate cancer specific mortality is 0.045 (95% CI = 0.040-0.052) and 0.023 (95% CI = 0.10-0.095) respectively (12).

While a trial comparing expectant management to prostatectomy and radiation therapy would be of great interest, we have elected not to include radiation therapy as a third treatment arm because of study cost, feasibility and sample size. Prior to randomization, patients will be informed about radiation therapy as a therapeutic option if they decline to enter this study.

#### E. Summary of Efficacy of Current Treatment Options

Drawing definitive conclusions regarding treatment efficacy from case series and the small clinical trials is difficult because of the variability in patient characteristics as well as differences in CAP stage and grade. These limitations were pointed out by Wasson and colleagues(12). They performed a structured literature review to define the clinical course of localized prostate cancer, the effectiveness of radical surgery and radiation therapy, and treatment complications. Because of methodological inadequacies of the available literature such as failure to stratify by grade of malignancy, extent of disease at the time of treatment and patient age as well as neglecting to identify patients lost to follow-up they concluded that "it is impossible for patients and their counselling physicians to make

informed choices based on knowledge of the benefits of radical prostatectomy, radiation or watchful waiting" (12).

A recent report utilized a decision analysis approach to assess outcomes from radiation, prostatectomy and expectant management for clinically localized prostate cancer (11). Their results demonstrate that even under optimistic assumptions the benefits of radical prostatectomy or radiation therapy are small. However, the efficacy varies depending upon assumptions of estimated interventional treatment efficacy and tumor metastatic rate. The authors state that "the only way to resolve the question of effectiveness [prostatectomy, radiation, or expectant management] is to obtain data on comparable patients by means of a sufficiently large clinical trial" (11). Until such a trial is completed they recommend that therapeutic choices should be based on interventional morbidity and patient preferences.

In summary, the results of these studies suggest that therapy reserved for palliative relief of symptomatic disease progression provides equivalent survival rates and quality adjusted life years to early intervention with prostatectomy or radiation. The uncertainty around these estimates indicate that a randomized trial comparing prostatectomy to expectant management is necessary to accurately determine the preferred strategy.

Prostatectomy offers the potential for complete removal of cancer. However, this intervention may be neither successful nor necessary. Expectant management, while not removing prostate cancer, avoids the morbidity and mortality from early intervention. Palliative therapy for symptomatic local disease progression with hormone manipulation and conservative urologic procedures has generally been successful. Thus, prevention or treatment of symptoms from the primary tumor is not an important indication for early intervention. While not commonly utilized in the United States, expectant management is frequently recommended for localized CAP in Europe.

Therefore, in 1993 the principal issue in prostate cancer remains the following unanswered question: is treatment necessary in whom it is possible and is treatment possible in whom it is necessary? The answer to this question requires the conduct of randomized controlled trials.

#### F. Comparison with Concurrent Studies

There are currently two randomized clinical trials investigating early interventional therapy versus expectant management for clinically localized CAP. A Danish study is comparing radiation treatment with expectant management. This study began in 1989, and has a projected sample size of 162 (30). The Swedish Oncologic Group is conducting a randomized clinical trial of lymph node dissection with subsequent prostatectomy if node negative versus expectant management (31). This study began in 1989 and has currently enrolled 220 patients with a projected sample size of 540. This study is only enrolling subjects with well differentiated CAP; i.e. those who will be less likely to develop disease progression with expectant management. Therefore, this smaller study is more likely to conclude that radical prostatectomy is of no benefit in clinically localized CAP. These studies lack sufficient power to detect a 40% increase in median overall survival or a 60% increase in prostate cancer specific survival from radiation or surgical therapy compared to expectant management. Additionally, surgical and radiation techniques used in Scandinavia are different than in the United States. Generalization of their results to patients in the United States will be difficult.

#### G. Screening Studies

The American Cancer Society-National Prostate Cancer Detection Project (ACS-NPCDP) is a multicenter, multidisciplinary study evaluating the use of transrectal ultrasound (TRUS), digital rectal examination (DRE), and prostatic specific antigen (PSA) for early detection of CAP in a large cohort of men not previously suspected of having prostate cancer (32). It does not have all-cause or prostate cancer specific mortality as primary outcome measures nor is this study of sufficient size to determine this outcome.

The National Cancer Institute Prostate, Lung, Colon, Ovarian Cancer Screening (PLCO) Project is a large multicenter trial being developed to investigate the effectiveness of DRE and PSA testing in the early detection and outcome of patients with prostate cancer (33). This study is designed to determine if early detection reduces mortality. Results from the PLCO project are unlikely to conclusively demonstrate that prostatectomy is superior to expectant management for localized CAP for the following reasons: 1) Patients not randomized to screening are likely to receive intermittent rectal examinations and PSA testing by their primary physician. This will dilute an expected benefit in the

screened group. A negative study might lead to the conclusion that screening and treatment with prostatectomy for CAP was of no benefit when one truly exists. 2) A positive study could not exclude a co-treatment effect as the reason for the improved survival in the screened group, (i.e. Patients screened for CAP are more likely to have medical therapy prescribed for comorbid conditions than patients not screened). 3) Results from the PLCO project will likely be confounded by lead and length time bias. Such bias is difficult to control for in screening studies and will make results susceptible to criticism. 4) Treatment of patients with localized prostate cancer detected in this study is not randomly assigned nor mandated. Conclusions regarding the efficacy of early intervention will thus be difficult. Therefore, a clinical trial comparing prostatectomy versus expectant management is necessary in addition to the current screening proposals.

### **III. STUDY HYPOTHESIS AND PRIMARY ENDPOINT**

The proposed study is a randomized clinical trial in patients with clinically localized prostate cancer designed to determine which of two treatment strategies is superior in reducing all-cause mortality: 1) radical prostatectomy and early intervention of subsequent disease persistence or recurrence or 2) expectant management with reservation of therapy for palliative treatment of symptomatic or metastatic disease progression.

### **IV. IMPORTANCE TO THE VA AND NCI**

Cancer of the prostate is the most frequently diagnosed cancer and the second leading cause of cancer related mortality. In 1993 it is estimated that 165,000 cases of CAP will be diagnosed and 35,000 men will die due prostate cancer. Because of continued improvements in life expectancy and a shift in the age distribution in favor of an older population, it has been estimated that, between the early 1980's and the year 2000, there will be a 37% increase in the number of prostate cancer-related deaths and a 90% increase in the number of cases of prostate cancer detected (34).

The growing magnitude of this health problem has heightened interest among patients, health care providers, and legislators in determining the preferred treatment for prostate cancer. Autopsy studies suggest a 30% prevalence of prostate cancer in the 28 million men 50 years of age or older. Thus, potentially 8.4 million men have prostate cancer. This undoubtedly overestimates the number of tumors

that will become clinically significant but reflects the potential disease burden if aggressive screening and treatment strategies are implemented.

A recent report addressing time trends, geographic variation and outcomes in Medicare patients having a radical prostatectomy for CAP indicated nearly a six-fold increase in the number of procedures performed since 1984. The American College of Surgeons Commission on Cancer compared the distribution of treatment modalities in patients with clinically localized prostate cancer in 1984 and 1990. Their findings confirmed the marked increase in the number of patients screened for prostate cancer and being offered early intervention. From a sample of 23,000 patients with newly diagnosed prostate cancer, treatment with radical prostatectomy in 1990 increased over threefold to almost five thousand (35). Therefore, it can be estimated that over 30,000 radical prostatectomy procedures are performed each year in the 165,000 patients with newly diagnosed prostate cancer. These statistics are not meant to imply that prostatectomy procedures are done inappropriately. Rather, they emphasize the growing utilization of radical prostatectomy, the impact this disease and its treatment have on United States health care, and the critical importance of conducting our clinical trial to be able to determine whether prostatectomy is superior to expectant management in patients with clinically localized CAP.

Recently, increased interest in CAP detection and treatment has developed in both the VA and NCI. The current PLCO screening study is sponsored by the NCI. It will provide valuable information on the effectiveness of early detection of prostate cancer. However, our clinical trial is necessary to determine whether subsequent intervention with radical prostatectomy provides improved survival in comparison to expectant management. Despite the large population of men at high risk for CAP served by the VA, the VA Preventive Medicine Program does not currently include prostate cancer screening because of the lack of available evidence that early detection and treatment is beneficial (36). Our study will provide evidence on the efficacy of early treatment of prostate cancer.

If the prevalence of CAP in the 8.6 million male veterans aged 50-70 is the same as reported in the screening studies of unselected men, then more than 2.3 million cases of CAP exist in this population (37). Presuming radical prostatectomy is performed in localized CAP, 891,000 veterans (248,000 Stage A2 and 643,000 Stage B tumors) would be potential candidates for radical prostatectomy. On a national level, a recent analysis estimated that the initial yearly cost for a national CAP screening and treatment program would range from \$4 to \$32 billion (38). This is between 0.5-6%



of the total United States' health care budget. Applying these screening and treatment cost estimates results in a potential yearly cost to the VA of \$1.8-\$13 billion.

Before widespread implementation of early detection programs can be advocated, it is critical to determine if treatment of localized CAP with radical prostatectomy improves survival. Our study will provide this information. If radical prostatectomy provides curative therapy in clinically localized CAP, then a large group of men with CAP would benefit from early detection and surgical treatment. Current recommendations from consensus panels, practice styles of primary care physician, and attitudes of patient will have to be modified to emphasize the importance of early detection and surgical referral for CAP. However, if expectant management provides equal or improved survival and quality of life, then many men are being subjected unnecessarily to screening and surgery with its attendant morbidity, mortality and cost.

## **V. RATIONALE FOR CHOICE OF POPULATION**

Our study is designed to enroll participants who are representative of patients in whom radical prostatectomy is generally performed. Prostatectomy is not routinely recommended in patients with a life expectancy less than 10 years. We have chosen an upper age limit of 75 because the median life expectancy of a 75-year old man is approximately 10 years.

We have included patients with clinical T1-T2 adenocarcinoma of the prostate regardless of histologic grading. Patients with clinically determined T1 and T2 tumors are believed to have localized prostate cancer and to be ideal candidates for surgical removal of the tumor. Patients with well differentiated prostate cancer have a low disease specific morbidity and mortality with expectant therapy. However, prostatectomy is also most likely to successfully remove the cancer in these individuals. Patients with poorly differentiated CAP have a high 10-year mortality rate regardless of treatment approach. The preferred therapeutic strategy in all of these patients is controversial and necessitates our clinical trial for definitive answers. We anticipate that approximately 10% of participants enrolled in this study will have poorly differentiated CAP. This is consistent with previous reports from case series of patients treated with radical prostatectomy or expectant management.

## VI. RATIONALE FOR STUDY DESIGN

Conclusions from previous studies are confounded by the small sample size, lack of control groups, the variability in tumor grade and stage, and patient populations enrolled. The potential benefit of either treatment strategy is large, however, because of the high prevalence of CAP. To avoid the limitations of previous studies, a randomized trial of prostatectomy versus expectant management is not only ethical but necessary in patients with clinical T1 and T2 disease. If prostatectomy is a treatment with even modest benefit, it could be valuable for patients with CAP, given the magnitude of the disease and the lack of effective therapy. It would be useful to know the magnitude of this benefit, in which patients it occurred, and what early detection strategies were most useful. However, if expectant management was shown to provide equivalent long-term survival and quality adjusted life-years, the associated morbidity and mortality of early intervention could be eliminated.

The study is designed to compare the current clinical practice strategy of radical prostatectomy with follow-up intervention for evidence of disease recurrence or persistence to an expectant management approach that reserves therapy for palliative relief of symptomatic or metastatic disease progression. The expectant management approach has as an emphasis minimization of therapeutic side effects. With increasing utilization of prostate cancer detection and treatment strategies, it is essential to determine if early detection and intervention with radical prostatectomy is effective.

We have chosen all-cause mortality as the primary outcome measure. The rationale for this decision is two-fold: 1) All-cause mortality is an unbiased and more easily defined endpoint than prostate cancer specific mortality. Because of death benefits claimed by families of veterans, ascertainment of all-cause mortality can be accomplished with 100% completeness. The National Death Index will ensure similar mortality data for nonveteran participants. 2) In the final evaluation, performing a radical prostatectomy is based on the belief that surgical extirpation of prostate cancer will not only free the patient of his cancer but also will prolong his life. Therefore, the ultimate goal of radical prostatectomy is to prolong life in individuals with CAP who are judged to be acceptable surgical candidates. If prostatectomy does not improve all-cause mortality, it is unlikely to be beneficial. Such rationale is supported by the fact that radical prostatectomy is not generally recommended for individuals who are likely to die from nonprostate cancer causes.

Our sample size is sufficiently large to be able to determine with a power of 90% whether radical prostatectomy results in a 15% improvement in overall survival (with an expected median survival of 15 years). This extremely powerful study design and sample size will provide conclusive evidence regarding efficacy of the two treatment strategies. Our study design and size will also be sufficient to determine if radical prostatectomy results in at least a 40% reduction in prostate cancer specific mortality.

## **VII. RATIONALE FOR THERAPEUTIC OPTIONS**

The primary purpose of the study is to compare the overall approach of immediate surgical intervention and follow-up therapy for disease recurrence or persistence to expectant management. The primary purpose is not to test the effect of a particular drug or intervention. Therefore, the types and indications for interventions were specifically written to allow maximum flexibility while still adhering to the primary study purpose.

We chose radical prostatectomy as the initial intervention option because it is the most common therapeutic strategy recommended for patients with clinically localized CAP. Radical prostatectomy as a primary treatment modality for prostate cancer has increased by almost 100% from 1984-1990 and can be expected to rise further as CAP is diagnosed earlier (35). Radiation therapy was not included as a treatment option because of sample size, cost, feasibility and data suggesting that radiation is not superior to prostatectomy (25-28).

The types and indications for interventions were designed to allow maximum flexibility in the radical prostatectomy arm consistent with current clinical practice. Therefore, we have allowed physician discretion in choosing the intervention and indication for postprostatectomy therapy. Patient outcomes will allow us to conclude if the general therapeutic approach of early detection with "aggressive" initial and follow-up intervention for disease persistence or recurrence is superior to expectant palliative management for symptomatic disease progression or evidence of metastatic spread.

The expectant management strategy utilizes specific predefined criteria to characterize symptomatic or metastatic progression. Therapeutic options in the expectant management strategy allow individual physician decision making while adhering to the principal of palliative therapies for

symptomatic progression utilizing the least morbid and costly approaches. Prostatectomy will be allowed in the expectant management group for palliative relief due to predefined symptomatic local disease progression that has failed to be relieved by more conservative interventions. Physicians and patients will be blinded to PSA results in the expectant management group to minimize treatment crossovers or interventions for nonsymptomatic disease progression.

Recent evidence suggests that treatment with total androgen blockade for metastatic prostate cancer prolongs survival (39, 40). Therefore, participants found to develop metastatic prostate cancer will be eligible for total androgen blockade therapy regardless of treatment arm. Participants randomized to prostatectomy will be included in the surgical arm even if prostatectomy is not performed because of positive lymph nodes or intercurrent events. Furthermore, many centers perform radical prostatectomy even in individuals with positive lymph nodes. Such a decision will be left to the discretion of the individual investigators and recorded. Finally, methods described above have been incorporated to minimize early prostatectomy in the expectant management group. If prostatectomy occurs for nonpalliative reasons these individuals will still be included in the expectant management analysis and classified as a protocol violation. Analysis by this "intention to treat" method is consistent with current clinical practice where patients undergo surgical exploration to determine if immediate intervention is indicated.

## **VIII. SECONDARY OBJECTIVES AND ENDPOINTS**

The primary hypothesis of this study is that all-cause mortality is similar in the two treatment strategies: radical prostatectomy and expectant management. Other objectives of this study include:

1. Effect on prostate cancer specific mortality. An adjudication committee, blinded to the treatment arm will assign a cause of death as being definitely, probably or not due to prostate cancer. The analysis will then investigate prostate cancer specific survival.
2. Effect on health status: The SWOG Prostate cancer specific quality-of-life scale, the AUA symptom and bothersome scale, and the SF-36 General Health Status questionnaire will be utilized to determine which of the two treatment approaches provide superior quality of life (41, 42).

3. Effect on disease recurrence: Patients in the prostatectomy arm will be monitored for evidence of disease recurrence by clinical examination, radiologic and laboratory testing. This will assess the efficacy of the initial intervention for complete tumor removal and prevention of disease recurrence.

4. Progression-free survival: The percent of patients who do not have evidence of prostate cancer progression as measured by clinical examination, radiologic and laboratory studies will be recorded. Local, regional and metastatic disease progression will be recorded. Severity of disease progression will be measured by functional status and health status instruments.

5. During the course of a 15-year study, it is likely that interest will emerge in additional laboratory studies not already included. Therefore, serum and tissue samples will be saved and frozen for serologic and pathologic determinants of CAP progression and mortality.

6. Determinants of prostate cancer progression and mortality: The subgroups of particular interest are defined by the following:

- a. Race
- b. Age
- c. Tumor stage
- d. Tumor grade
- e. Tumor volume
- f. Family history of CAP
- g. PSA level and rate of change in PSA
- h. PAP level and rate of change in PSA

7. Use of the Charlson comorbidity index to predict all-cause and prostate cancer specific mortality (43).

## **IX. STUDY DESIGN**

We will conduct a randomized controlled clinical trial comparing two management strategies for clinically localized CAP: 1) radical prostatectomy and early intervention for cancer persistence or recurrence versus and 2) expectant management with palliative therapy reserved for symptomatic or metastatic disease progression.

## **X. PATIENT SELECTION CRITERIA**

### **A. Inclusion Criteria:**

To be eligible for the trial, subjects must meet the following criteria:

1. Age 75 years or younger
2. Clinically localized (T1a, b, c-T2a, b, c, NX, MO) adenocarcinoma of the prostate
3. Diagnosis of prostate cancer within the previous 6 months

### **B. Exclusion Criteria:**

1. Significant coexisting medical conditions that are acute, debilitating or expected to result in a life expectancy less than 10 years or place the patient at unacceptable surgical risk (e.g. evidence of nondermatologic malignancy within the past five years, severe pulmonary, cardiac, renal, or hepatic impairment, myocardial infarction within six months, unstable angina, dementia, or other debilitating illness).

2. Prior surgical (except TURP), irradiation, hormonal or chemotherapy for CAP.

3. Laboratory abnormalities that in the opinion of the Participating Investigator are expected to result in a life expectancy less than 10 years.

4. Evidence of clinically nonlocalized prostate cancer
  - a) PSA > 50 (if on finasteride within the previous 3 months, PSA > 25)
  - b) Bone scan consistent with metastatic disease

c) Other imaging or laboratory studies performed at the discretion of the Participating Investigator indicating that prostate cancer is nonlocalized.

5. Current use of any of the following medications: estrogens, 5' alpha-reductase inhibitors, antiandrogen drugs.

6. Inability or unwillingness to give informed consent.

7. Reasonable likelihood that the patient cannot be followed during the study period.

8. Participation in another intervention research study.

## **XI. PATIENT RECRUITMENT**

Recruitment of participants will be through veterans organizations, and Medicine, Urology, Oncology and Prostate Cancer Screening clinics. Community based efforts will include radio, television and newspaper advertisement. Participating Investigators and clinic coordinators will develop outreach programs with community internists, urologists, oncologists and Prostate Cancer Support Groups. The patient and family educational videotapes will be provided to these individuals and groups to enhance knowledge of the study and provide education about prostate cancer.

Under the direction of the Participating Investigator, each center will review the urologic logs, operating room lists, pathology and laboratory records and cancer registry to identify all patients with CAP who may be eligible for randomization. All eligible patients will be offered randomization and encouraged to view an informational videotape developed for the study. Participating sites will complete and report to the coordinating center a prescreening prostate cancer log with a list of all patients with prostate cancer. Information on this list will include: (a) subjects eligible and randomized; (b) subjects eligible but not randomized; (c) subjects with clinically localized CAP but who are ineligible because of comorbidities. A list of the initial intervention provided to nonrandomized subjects (prostatectomy, expectant management, hormonal therapy or radiation) will be maintained. A previous surgical trial has utilized this method to ensure adequate enrollment and representativeness of participants (44).

## **XII. PATIENT DIAGNOSIS**

Study eligibility will require a pathologic diagnosis of prostate cancer. This will be based on a histologic diagnosis of CAP from core needle or TURP biopsy specimens. Prior to randomization, specimens will be interpreted by the participating centers' local pathology laboratory and the presence of CAP confirmed. For standardization purposes a centralized reading of slides from biopsy (and prostatectomy) specimens will subsequently be performed by Dr. Thomas Wheeler at Baylor College of Medicine in Houston, Texas. To facilitate patient enrollment, central reading will not be required prior to patient randomization. The central pathology report will provide the final histologic grading. The Gleason grading system will be utilized.

### **A. Staging of CAP**

The TNM staging system will be utilized (45). Both clinical and pathologic staging will be recorded. Eligibility will be based on clinical staging indicating clinically localized CAP. Patients must be prepared to undergo prostatectomy within 6 weeks after registration. Patients will be clinically staged by rectal examination, PSA and bone scan. Patients with evidence of extra-prostatic disease will be excluded. An elevated prostatic specific antigen level (PSA) will not exclude the patient unless the level is markedly elevated ( $> 50$  ng/dl). Use of imaging methods such as transrectal ultrasound, CT or MRI scans will be at the discretion of the individual centers. These will not be required for enrollment into this study but the use of such methods will be recorded. Surgical prostate specimens will be sent en bloc to the central pathology laboratory for review and confirmation.

### **B. Clinical Staging System:**

T1: Clinically inapparent tumor, not palpable nor visible by imaging

T1a:  $\leq 5\%$  of TURP specimen and Gleason score  $\leq 7$

T1b:  $> 5\%$  of TURP or Gleason score  $> 7$

T1c: Identified by systematic biopsy performed e.g. because of an elevated PSA

T2: Palpable or visible tumor confined within the prostate

T2a: Palpable nodule (or visible lesion if TRUS performed)  $\leq 1/2$  lobe and confined to the prostate



- T2b: Tumor involves more than half of a lobe but not both lobes, confined  
T2c: Tumor involves both lobes

### **XIII. SCREENING PROTOCOL (Figure 4)**

#### **A. Prescreening Phase**

Potential subjects (men aged  $\leq 75$ ) will be identified through various sources:

- a) Urology, Medical, Oncology, Prostate Cancer Screening clinics
- b) Community Prostate Cancer Support Groups
- c) Pathology and urology logbooks of all prostate biopsies or specimens
- d) Laboratory lists of PSA and PAP values
- e) Referrals obtained from community physicians or media advertisement

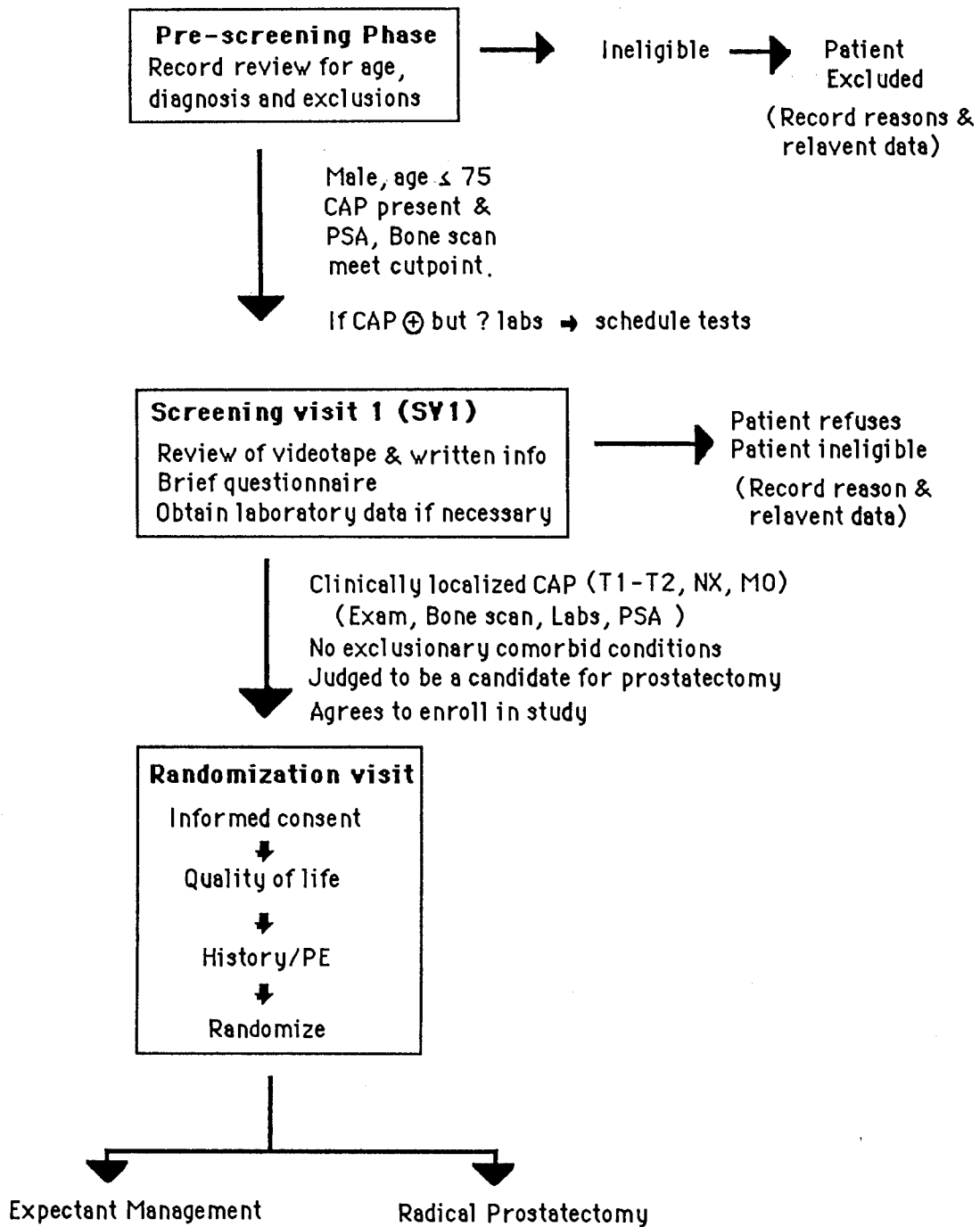
The records of potential subjects will be reviewed and all patients with a confirmed or suspected diagnosis of prostate cancer will be identified. Potentially eligible subjects will be invited to an initial screening visit. All patients with a new diagnosis of prostate cancer will be recorded on the screening log.

#### **B. Screening Phase**

The study will be explained to the individual and family members. They will be encouraged to review the educational study videotape and written materials on prostate cancer. After review of this information, the patient will discuss therapeutic options with the Participating Investigator. If necessary, the patient will be scheduled for laboratory and radiologic tests to confirm the diagnosis of prostate cancer and evaluate the extent of his disease. Patients declining study enrollment will have treatment offered by their primary physician. Screening data will be collected on all patients with prostate cancer: (a) study ineligible; reason for ineligibility recorded, (b) study eligible but refused; reason for refusal recorded, (c) study eligible and enrolled. This will include: age, gender, tumor stage and grade.

Figure 4

### SCREENING PROTOCOL



### C. Baseline Visit

Eligible, consenting subjects will return for the baseline visit at which time the following will be performed:

1. History and quality-of-life questionnaires
2. Physical examination including DRE, weight and height.
3. Laboratory studies at the discretion of the PI for evaluation of CAP.
4. The Charlson Comorbidity index to characterize comorbid conditions.

## **XIV. INFORMED CONSENT PROCEDURES**

At the second screening visit, informed consent will be sought from eligible subjects by the Participating Investigator. The subject may choose to either read the description of the study or have it read to him. He will be given an opportunity to ask questions, consult with others, and/or have time to "think it over." If the patient consents he will sign, in the presence of a witness, VA Form 10-1086 which contains the information about CSP #407. Form 10-1086 will be placed in the patient's hospital chart with copies to the patient, the patient's study file, the Study Co-Chairman and the coordinating center.

Prior to randomization all subjects will watch the patient introductory information videotape that discusses CAP, treatment options, risks and benefits. This videotape also provides information about the study. The Participating Investigator will be available to answer questions that the patient and/or his family may have regarding the written informed consent, the information videotape and the study.

## **XV. TREATMENT REGIMEN AND RANDOMIZATION (Figure 5)**

Patients will be randomized to radical prostatectomy or expectant management. Patients will be stratified by medical center. Baseline data will include clinical stage and grade of the biopsy specimen, PSA level, age, race, presence of prostatic symptoms, health status, demographics, history of other medical conditions, Charlson Comorbidity index, and family history of CAP.

**TABLE 3  
STUDY EVALUATIONS**

PARAMETERS	FREQUENCY
CAP DIAGNOSIS	PRESCREENING LOG: CHART REVIEW/BIOPSY/REFERRAL
<u>ELIGIBILITY</u>  PI INTERVIEW/DISCUSSION VIDEO CONFIRMATION TESTING: PSA, BONE SCAN	SCREENING VISIT
<u>ENROLLMENT</u>  INFORMED CONSENT HISTORY/PHYSICAL CLINICAL STAGING QUALITY-OF-LIFE/HEALTH STATUS QUESTIONNAIRE	AT RANDOMIZATION
<u>FOLLOW-UP</u>  HISTOPATHOLOGIC GRADING <u>CLINIC VISITS</u> CLINICAL STAGING PSA (CENTRAL LAB) QUALITY-OF-LIFE/HEALTH STATUS QUESTIONNAIRE HISTORY/PHYSICAL BONE SCAN TREATMENT FOR CAP DEATH REPORT	POSTOP (SURGERY GROUP ONLY) 6 WEEKS, 3,6,9,12 MONTHS, THEN EVERY 6 MONTHS  ANNUALLY AS PROVIDED WHEN IT OCCURS

In the expectant management group, interventions will be directed at providing palliative relief of the patients presenting symptoms. Initial management considerations will utilize procedures with the lowest morbidity. Patients will not be treated for asymptomatic disease progression/recurrence or evidence of asymptomatic increases in PSA unless there is evidence of metastasis. Hormonal therapy will be the first line treatment for patients with disease progression requiring nonmechanical therapy. Patients who continue to progress or do not respond to hormonal therapy will be treated with radiation or chemotherapy. Prostatectomy is an option for participants in the expectant management group that have symptomatic local disease progression (defined as recurrent and persistent gross hematuria or bladder outlet obstruction) despite recurrent use of TURP, stents and alpha blockers. The operations manual will clearly specify the criteria required for radiation or prostatectomy in the expectant management group. The Chairman's office will review all prostatectomy or radiation procedures performed and notify centers violating protocol.

Disease progression is defined as follows:

a) Asymptomatic local disease progression/persistence:

- i. New or enlarging mass on DRE, TRUS or other imaging modality
- ii. Persistent tumor despite prostatectomy

b) Symptomatic local disease progression:

- i. Hematuria secondary to prostate cancer progression
- ii. Bladder outlet obstruction due to prostate cancer progression
- iii. A change in the AUA symptom bothersome score due to prostate cancer of 3 points or indicating moderate-severe symptoms ("a lot" or "unhappy")
- iv. Rise in laboratory tests determined to be consistent with prostate cancer: e.g., rise in creatinine, AST, bilirubin to 2X baseline

c) Symptomatic regional disease progression:

- i. Pelvic pain secondary to prostate cancer
- ii. Lymphedema secondary to prostate cancer

d) Asymptomatic regional disease progression:

- i. Hydronephrosis on imaging study with evaluation prompted by creatinine elevation to twice baseline or other evidence of regional progression

e) Asymptomatic metastatic disease progression:

- i. Changes in laboratory tests due to prostate cancer including Hgb < 10.0; abnormal AST, PAP, Bilirubin.
- ii. Abnormal bone scan consistent with prostate cancer
- iii. Radiologic evidence of metastatic disease including bone or chest roentgenograms or abdominal.

f) Symptomatic metastatic disease progression:

- i. Nonpelvic bone pain secondary to prostate cancer

- ii. Decrease in functional status category due to prostate cancer
- iii. Other symptoms (e.g., weakness, nausea, confusion) that in the opinion of the investigator are judged to be due to metastatic CAP.

g) Asymptomatic progression of tumor biomarkers

- i. Increasing or persistent PSA
- ii. Abnormal Prostatic Acid Phosphatase

D. Health Status Surveys

The Prostate Cancer Specific and Overall Quality-of-Life questionnaires developed by Moinpour and administered in previous prostate cancer studies will be utilized (41). They have been demonstrated to have face validity and reproducibility. These surveys will be self-administered prior to randomization and every 6 months. The Prostate Cancer Quality-of-Life and Health Status questionnaire developed by Wennberg and Barry will be utilized to further assess prostate cancer and therapy related symptoms. The AUA prostate symptom and bothersome index will be utilized to assess for prostate specific symptoms (42). The SF-36 health status survey will be employed to assess overall health status including a global assessment of functional status (Table 3).

**XVII. ADHERENCE TO ASSIGNED REGIMEN INCLUDING USE OF VIDEOTAPES**

Centers will be selected, in part, on their willingness to offer randomization to patients fulfilling study criteria. Participating Investigators and Study Coordinators will attend introductory and annual meetings to receive education and review of the study protocol, recruitment, and adherence. In particular, investigators and coordinators will be provided information on patient and family counselling for asymptomatic disease progression.

Patients and family members will be provided educational videotapes and written materials prior to randomization. This information will focus on controversies in the treatment of prostate cancer. Issues related to patient anxiety regarding asymptomatic disease progression in the expectant management group will be addressed. At the annual visit, all participants will review the entry videotape and receive additional written and verbal information about the study and CAP. All centers will be monitored for adherence to study protocol. This will include: (a) number of patients randomized, (b) a log of all patients

with prostate cancer, (c) completion of intervention forms to document type of intervention and reason for intervention in either treatment arm and (d) number of patients violating protocol (e.g. patients in the expectant therapy arm being treated with radical prostatectomy or "curative" radiation therapy). To decrease crossovers in the expectant management strategy, PSA assays will be performed in a central laboratory and only be unblinded and reported if there is a marked rise in PSA levels to  $> 50$  ng/mL. Participants will be informed that an increase in a PSA level may indicate disease progression but in the absence of symptoms does not require treatment. All protocol violations will be reviewed by the Co-Chairmen and Data Monitoring Board. Centers will be notified of these violations. Excessive protocol violations will be an indication to terminate centers from the study.

## **XVIII. ENDPOINTS**

All cause mortality is the primary study endpoint because the decision to recommend surgery over expectant therapy for patients with CAP is ultimately based on whether prostatectomy will improve patients overall survival. Death records, Veterans death benefits, the National Death Index and abstraction of medical records will be utilized in ascertaining both all-cause and CAP specific mortality. Secondary endpoints include CAP related mortality defined as mortality due to: 1) widespread CAP, 2) any procedure performed during pre-operative evaluation for radical prostatectomy or other intervention for prostate cancer and 3) occurring within 30 days of surgery for CAP. Assignment of cause of death will be made by the Endpoint Committee blinded to the initial treatment assignment.

Prostate cancer specific morbidity will also be determined. This will include complications resulting from treatment or progression of prostate cancer. CAP morbidity will be classified as: a) local/regional: arising from the prostate tumor; hematuria, pelvic pain, lymph edema, bladder outlet obstruction, b) arising from metastatic prostate cancer; nonpelvic bone pain, weight loss, anemia, etc., c) decrease in functional status as assessed by the previously validated SWOG CAP-Functional Status and Health Status Questionnaire and d) complications from surgery including; incontinence, impotence, colostomy.

Effect on health status will be assessed by the SF-36 General Health Status scale, the AUA prostate symptom and bothersome scale and the prostate cancer specific health status questionnaires. The overall and symptom specific scores during the course of the study on each of these instruments will be compared between the two treatment groups.

Disease recurrence will be routinely assessed by digital rectal examination, PSA and annual bone scans. Evidence of disease recurrence will be classified as symptomatic or asymptomatic and whether there is evidence of local, regional or metastatic prostate cancer. Patients who do not have evidence of disease progression or recurrence by these methods will be classified as having progression-free survival.

A central histopathologic reading center will be utilized for uniform reading of biopsy and prostatectomy specimens. This will provide a central reading of all specimens for baseline characterization of participants and for further analysis regarding prognostic variables (e.g. distribution of Grade and Stage between prostatectomy and expectant management group; predictors of all-cause and prostate cancer specific mortality between the two groups).

A central laboratory will also be utilized to perform PSA measurements. The following PSA parameters will be utilized for endpoints: a) rate of change in PSA between the two treatment arms, b) percent of participants in the prostatectomy group that have undetectable PSA following surgery, c) percent of participants in prostatectomy group who develop newly detectable PSA, d) percent of participants in expectant management group with PSA > 50 and e) mean baseline PSA in prostatectomy group versus expectant management group. Serum will be stored for future analysis for predictors of disease specific mortality.

Additional baseline data will be utilized to characterize and predict outcomes in participants. This will include race, age, family history of CAP, smoking history, Charlson Comorbidity index, and tumor stage and grade.

It is expected that up to 30% of patients with clinically localized CAP will have pathologic evidence of nonlocalized disease at surgery (46). These patients will be included in the surgical group and analyzed via intention to treat methods. Because of the large sample size, it can be expected that randomization will provide equal numbers of pathologically nonlocalized disease in both treatment groups, though it will not be possible to confirm this. We will compare treatment effectiveness in subgroups (including patients with pathologically confirmed localized disease and histopathologic tumor grade) with the overall study population to define subgroups in whom treatments provide varying efficacy. The decision for surgical intervention is based on clinical not pathologic determination of disease localization. Therefore, we utilized clinical estimates, rather than pathologic determination of disease localization, to determine our sample size.



Our clinical staging criteria are consistent with current medical practice for establishing that a patient is likely to have pathologically localized disease and is therefore a candidate for radical prostatectomy. Our goal was to maximize the likelihood that clinical staging criteria would accurately predict pathologic staging while still reflecting the current medical practice pattern. We will monitor the percent of patients with clinically localized disease found to have pathologically nonconfined cancer. If the percent is found to exceed 30%, the Executive Committee and Data Monitoring Board could recommend that enrollment criteria be altered to improve the correlation of clinical and pathologically localized disease. Review of patient enrollment regarding tumor histology will also be evaluated to ensure adequate representation (approximately 10%) of participants with poorly differentiated (Gleason score 7-10) CAP. Due to the large sample size, stratification by tumor grade should not be required.

## **XIX. STATISTICAL REVIEW**

### **A. Study Design and Outcome Measures**

This study has been designed as a prospective randomized controlled clinical trial to compare two management strategies for clinically localized CAP: radical prostatectomy and early intervention for cancer persistence or recurrence; and, expectant management with palliative therapy reserved for symptomatic or metastatic disease progression.

The primary objective of this study is to evaluate the effectiveness of radical prostatectomy with aggressive management versus expectant management limited to symptomatic treatment in reducing mortality in patients with clinically localized cancer of the prostate. Patients who meet inclusion/exclusion criteria and who sign informed consent will be randomly assigned to one of the treatment approaches. Separate randomization lists will be prepared for each of the participating centers and random assignment will be by telephone to the Perry Point CSPCC. Follow-up clinic visits will be scheduled at 6 weeks, 3, 6, 9 and 12 months after randomization and every 6 months thereafter. It will be necessary to maintain a blind on PSA tests in the Expectant Management Group which will be evaluated centrally. The study will otherwise be unblinded.

The primary outcome measure for this study is death from any cause, i.e., all-cause mortality. In order to further clarify the direct effects of treatment on prostate cancer mortality, each death will then be classified as either death from prostate cancer, death from other cancer or death from other causes. This will be done based on documentation of each death including death certificate, autopsy report, patient chart and other medical records which will be submitted for independent blind review by a study Endpoint

Committee. This committee will have the primary responsibility of correctly classifying each death as CAP related or from other causes.

In addition to the primary outcome, several secondary endpoints related to tumor progression and tumor related symptoms as well as quality of life will be of interest. These will be based on regular follow-up assessments that include: digital rectal exam, urologic symptoms, bone scan, serologic samples for central laboratory evaluation, pathologic/histologic review, PSA testing, and quality-of-life questionnaires. These measures have been discussed in detail above and the detailed plans for analysis are reviewed in the Biostatistical and Research Data Processing (Appendix BRDP) section in Volume II of this proposal.

**B. Sample Size and Study Duration**

The primary outcome measure for this study and the one on which sample size estimates will be based is all-cause mortality. The most current and complete structured literature review of treatment for localized prostate cancer was published coincidentally with the second planning meeting for this study (12). The lead author of that review was a member of the Planning Committee and the estimates and assumptions below are consistent with both the results of that paper as well as other unpublished series reviewed during planning. Based on review of these previous studies, the current best estimate of median survival for patients in the expectant management group is 15 years, i.e., the 15-year survival rate is 50%. In deriving sample size estimates, it is expected that the usual assumptions regarding patient risk (i.e., survival times are exponentially distributed) and patient entry (at a uniform rate during the intake period) that are common to studies involving progressive chronic diseases will also apply in this study. Given these assumptions, the required sample size can be determined by the following method which was developed by Gross and Clark (47) and generalized by Lachin (48,49).

$$SAMPLE\ SIZE = (Z_{\alpha} + Z_{\beta})^2 [F(\mu_e) + F(\mu_c)] + (\mu_e^{-1} - \mu_c^{-1})^2$$

where

$$F(\mu_i) = \mu_i^{-2} \left[ 1 - \frac{\mu_i (\exp[-(T-T_o)/\mu_i] - \exp[-T/\mu_i])}{T_o} \right]^{-1}$$

and where

- $Z_{\alpha}, Z_{\beta} =$  Standardized normal deviate for Type I error rate of  $\alpha$ , and Type II error rate of  $\beta$ .
- $\mu_e, \mu_c =$  mean survival times in the experimental (here, radical prostatectomy) and control (here, expectant management) groups, respectively.

- $T_0$  = time (months) such that patient recruitment begins at time 0 and ends at time  $T_0$ .
- $T$  = time (months) such that  $(T-T_0)$  represents the minimum follow-up of the last patient randomized for the purpose of final analysis. This method assumes patients will enter the trial uniformly over the period  $(0, T_0)$  and all patients will be followed through time  $T$  where  $(T-T_0)$  is referred to as a "continuation period".

This approach offers a number of advantages. It provides a means of incorporating survival times as the basis of sample requirements and relates these to both length of intake and length of a follow-up period beyond the end of intake. While based on mean survival time it can be modified to obtain sample requirements in terms of median survival by noting the constant multiple relationship between the mean and median of the exponential distribution (where Median = Mean \* ln2). Further, estimates can be derived for clinical effects of detectable interest both in terms of either increases in median survival or the corresponding increases in proportion surviving (or conversely, reductions in mortality rates) at the median survival time. This is based on the definition of the hazard rate,  $\lambda$ , in terms of the proportion surviving,  $p$ , given by  $\lambda = -\ln(p)/t$ , for a given time,  $t$ , under the exponential properties of constant and proportional hazards (47). Sample size estimates have been derived for several levels of parameters of interest including percentage increase in median survival (with the corresponding reduction in cumulative mortality rate), length of intake period, length of follow-up after intake ends, and statistical power for two-tailed alpha (Type I error) of 5%, assuming median survival of 15 years. These estimates are presented in Table 4. In general, for fixed levels of detectable clinical effects, decreasing either the intake or follow-up period (or both) has the effect of increasing sample size requirements and increasing study costs. In reviewing such factors as length of study, availability of centers, the expected per center yearly enrollment rates (estimated at 8-12 patients per year), the importance of long-term follow-up for prostate cancer and the costs associated with respective trade offs related to combinations of these factors, the Planning Committee has decided on a 15-year study comprised of a 3-year intake period and a 12-year follow-up period. Further, the power of the study (90%) should be sufficient to detect at a minimum a clinical effect of a reduction in mortality rate of 15% (25% increase in median survival). From Table 4, it can be seen that a recruitment goal of 2000 patients, 1000 on each treatment arm, will satisfy these requirements. This goal is quite conservative in the view of the Planning Committee in that this study is powered to detect relatively small but clinically important clinical effects. The results should be convincing to the medical community one way or the other. That is, a 15-year study of 2000 patients showing no obvious benefits for radical prostatectomy will provide a conclusive answer to the perplexing dilemma for which the study was developed. As an example of the small clinical effects that the study has been designed to detect, simulated survival curves for three samples sizes from Table 4 appear in Figure 6 where they are contrasted with a curve centered at 50% at 15 years.

Table 4

Number of Patients per Treatment Group for Different Levels of Statistical Power, Length of Intake, Length of Follow-up for Type I Error of 5% (2-Tailed) Assuming Median Survival of 15 Years

Percentage Reduction in Mortality Rate		Corresponding Increase in Median Survival Time	Power	Intake (Years)											
				2				3				4			
%	From 50% to	Delta (%)		10	11	12	10	11	12	10	11	12	10	11	12
10	45.0	16	85	2199	2056	1936	2126	1995	1883	2059	1938	1835	2059	1938	1835
			90	2573	2406	2265	2488	2334	2204	2410	2268	2147	2410	2268	2147
15	42.5	25	85	977	913	859	944	885	836	914	860	814	914	860	814
			90	1143	1068	1005	1105	1036	978	1070	1007	953	1070	1007	953
20	40.0	36	85	552	516	485	533	500	472	516	486	459	516	486	459
			90	646	603	568	624	585	552	604	568	538	604	568	538
25	37.5	47	85	355	331	311	343	321	303	332	312	295	332	312	295
			90	415	388	364	401	376	354	388	365	345	388	365	345

Figure 6

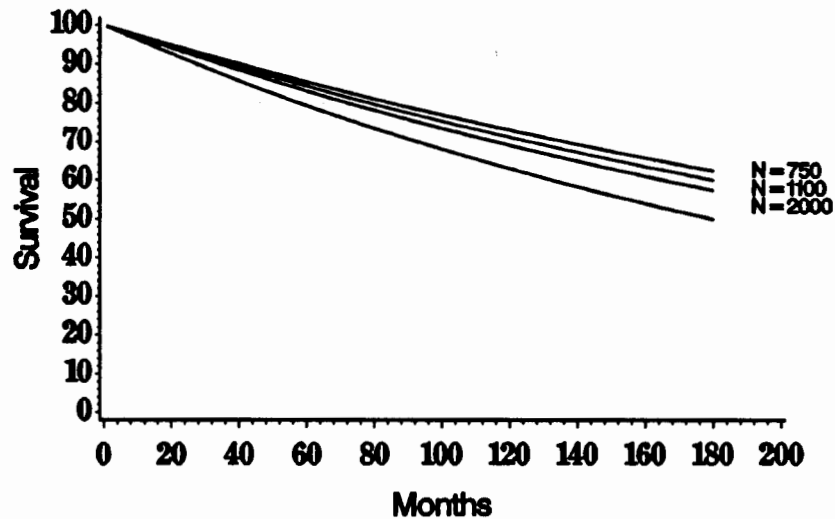


Figure 6: Simulated Survival Curves for Three Select Sample Sizes  
Relative to Survival of 50% at 15 Years

A secondary but important endpoint that will also be evaluated is cancer specific mortality. It has been estimated by the Planning Committee that 15-year cancer specific mortality would be expected to range from 15%-25%. The committee also decided that a convincing study would be one that could detect at least a 50% reduction in cancer specific mortality. The sample size calculations were repeated as above for a number of levels of parameters related to cancer specific mortality. These studies showed that the goal of entering 2000 patients is quite conservative with respect to cancer specific mortality. That is, if the lower estimate of 15% mortality were used (resulting in the highest sample size), the study is sufficiently powered to detect reductions in mortality of at least 40%.

Because of the availability of benefits systems and/or death registries and the advantages they provide in tracking patients, it is expected that the date of death will be determined for all patients. The study will require the enrollment of 667 patients per year during the intake period indicating that, conservatively, 60-80 participating centers will be required. In order to mount a clinical trial of this size, the study has been planned as a joint collaborative trial involving both the VA Cooperative Studies Program and the National Cancer Institute, which through its infrastructure of national and regional oncology groups, ensures the feasibility of completing the study. Within the VA, a great deal of interest has been expressed in participation in this study. At the time of submission, more than 40 VA centers have expressed an intention to participate. These centers are listed in Volume II of this proposal (see Participation).

### C. Statistical Analysis

The primary outcome variable for this study is all-cause mortality, death from any cause. The comparison of the relative effectiveness of the two treatment management approaches, radical prostatectomy and expectant management will be based on a survival analysis of time to death as measured from the time of randomization. Survival curves for each of the treatment groups will be estimated with Kaplan-Meier methodology and treatment group comparisons will be based on the logrank test. The analysis will be conducted on an "intention to treat" basis.

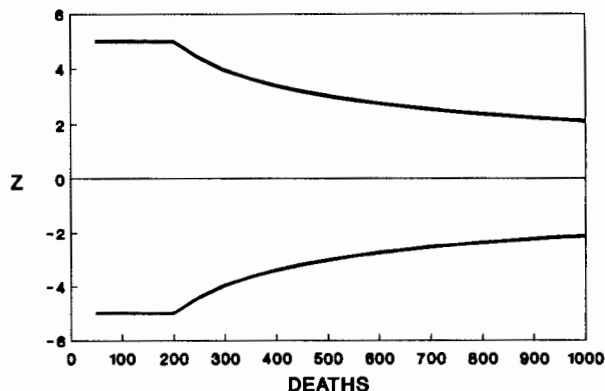
Each death will subsequently be classified with respect to the direct effects of prostate cancer. Treatment groups will then be compared as in the primary analysis outlined above but based on mortality due to prostate cancer. In addition to the primary analysis of mortality, patients will be monitored routinely during follow-up on a number of secondary measures. These are related primarily to tumor recurrence or progression with related symptoms and include physical symptoms, quality of life, and types of treatment that have been provided for CAP symptoms. For a number of these measures, the primary objective of data analysis will be largely descriptive. In the radical prostatectomy arm, recurrence will be of primary interest and summary statistics regarding associated rates and symptoms will be developed. In the expectant management arm, tumors will remain intact and summary statistics will be developed for progression and metastatic rates along with statistical characterization of associated symptomatology. Likewise, since the two treatment arms require essentially different applications of available symptom management procedures, both in timing and amount, the strategy will be to develop statistical summaries of treatment in order to characterize the two study treatment arms. Descriptive statistics for surgical events including types and associated rates of complications will be developed. An important consideration in evaluating the study interventions is the overall quality of life as experienced by study patients. The study measures include a number of standard scales for assessing quality of life and direct comparisons between treatment groups will be performed. The scales are usually ratings and will be compared by analysis of variance procedures. Both individual scales and derived composite scores will be of interest and therefore subject to this analysis. The complete details of the data analysis including presentation formats are provided in the Biostatistical and Research Data Processing (Appendix BRDP) section in Volume II of this proposal.

### D. Interim Monitoring and Repeated Significance Testing

The responsibility for independent monitoring of this proposed study once ongoing will be assumed by the Data Monitoring Board. This committee meets periodically in order to review accumulating

results in order to determine whether the study should continue. The current schedule is to meet at start-up, after nine months, and annually thereafter. When repeated significance tests are performed on accumulating outcome data as part of a "stopping rule" or periodic monitoring function, the overall Type I error rate for the study can change dramatically. This statistical problem has received considerable attention in the literature and the reviewer is referred to general texts (50,51) for a detailed discussion and additional references. Briefly, it can be shown that as the number of repeated tests increases so does the overall Type I error rate. For example, the overall Type I error rates for 5, 10, and 20 repeated tests all at the 5% level of significance are 14%, 19% and 25% respectively (52). Several different methods have been developed for dealing with this problem (50), all of which rely on adjusting the significance levels of the individual tests so that overall protection is maintained at a prespecified level. It will be proposed that as part of this protocol, a monitoring rule be adopted as follows. At each of its annual meetings, the Data Monitoring Board will review the results of the primary analysis. Specifically, the logrank statistic will be computed after every 50 deaths and will be compared to a set of monitoring boundaries derived from methodology proposed by Lan and DeMets (53). This approach produces boundaries such that if the p-value of the logrank statistic exceeds the p-value associated with the boundaries, the committee should recognize that an important "warning" has been signaled. That is, there is reliable evidence of early differences that may be conclusive upon further review and in fact, lead to a recommendation for early termination. The Lan-DeMets procedure produces decision boundaries that are quite conservative over the first several "looks" and which gradually converge to the nominal alpha levels as the final "look" is approached. Figure 7 provides as an example a graphical presentation of Lan-DeMets boundaries for 20 "looks".

FIGURE 7



## **XX. FEASIBILITY AND COLLABORATION WITH THE VA AND NCI**

A total of 2000 patients will need to be enrolled in this study. Estimates from the Patterns of Care Study indicate that approximately 50,000 radical prostatectomies are performed annually. Current data indicate that 66% of patients with Stage A and 17% of Stage B prostate cancer have expectant management for their prostate cancer.

We anticipate the number of patients eligible for prostatectomy to increase as the frequency of screening for CAP increases. In fiscal year 1992, the patient treatment file (PTF) indicated that 1,530 radical prostatectomies were performed at VAMC's. This represents a 12% increase from 1991. Our discussion with participating medical centers indicate that the PTF underestimates by as much as 5-fold the number of prostatectomies performed. Additionally, these data do not include information about subjects with clinically localized CAP who received radiation or expectant management as initial therapy who may be eligible for this study. Therefore, the number of patients from VAMC's who will be eligible for this study will be greater than those having received prostatectomy.

Based on previous surgical case records, an active screening program will not be necessary at VAMC's to detect sufficient number of cases of clinically localized CAP for this study. We estimate that participating VAMC's will be able to enroll an average of 10 patients/VAMC/year or 30 patients/VAMC/study. This results in less than one patient per month assigned to prostatectomy and should be feasible at VAMC's. This would result in 1,350 patients enrolled from 45 VAMC's. Centers concerned that participation will reduce the number of prostatectomies available for resident training can be reassured that on average only five patients/year who are candidates for prostatectomy would not receive this operation.

The National Cancer Institute, through the Southwest and Eastern Oncology Groups (SWOG and ECOG) Cancer And Leukemia Group B (CALGB), has a large network of medical centers (both university and community based) that have successfully recruited for many clinical trials. We have received a formal commitment for participation and support from Dr. Richard Kaplan of the National Cancer Institute and the Prostate Organ Chairmen of SWOG, ECOG and CALGB (See letter and Appendix). Using 35 SWOG/ECOG/CALGB sites would require enrolling 6.2 patients/NCI center/year at NCI sites (18.6 patients/NCI center/study). Many VA investigators have SWOG/ECOG/CALGB affiliation. This will facilitate patient enrollment and ease operational complexity.



If recruitment is slower than anticipated a fourth year of enrollment could be added without additional expenses because of our use of a capitation system. This would result in a mean follow-up of 13 years (rather than 13.5 years) and will have little effect on study power (See Table 4 in Sample Size Section). If a fourth year of enrollment was necessary, centers would then have to enroll at a rate of 7.5/year at VAMC's and 4.6 patients/year at NCI sites.

## **XXI. VA AND NCI COLLABORATION AND FUNDING OF CENTERS**

This proposal is a joint collaboration between the Department of Veterans Affairs Cooperative Studies Program and The National Cancer Institute. Representatives from both the VA and NCI have served on the planning committee and have approved the proposal, the collaborative agreement and the funding mechanisms outlined below.

We have proposed a capitation system as the most feasible method for reimbursement. All participating centers have past experience in conducting clinical studies using similar reimbursement methods. They have data managers in place that can assist with data collection. Data collection forms have been simplified to collect only essential information for the main outcome measures.

We will reimburse centers for efforts related to patient recruitment, enrollment and follow-up. This will include funding for completion of a monthly Participant Prescreening Log, eligible participants viewing the informational introductory videotape, randomized participants, follow-up visits and the costs for processing and shipping of samples specifically required for this study. The exact method of reimbursement will be outlined in greater detail in the budget justification section.

We have reviewed other funding options such as full- or part-time data managers at each center. Because of the large number of centers required for this study, the relatively few patients enrolled per center and the limited additional follow-up required for study evaluation beyond usual clinical practice, we do not believe that a dedicated data manager could be justified.

This should be feasible given the expected total enrollment of 10-50 patients/per center and scheduled biannual visits. We anticipate that unscheduled visits will result in an average of 4 visits per year.

The patient population served by the VA is representative of those who would most benefit from and in whom this study is most feasible. The Death Records maintained by the VA will ensure essentially

100% follow-up for mortality statistics. Patients followed in the VAMC's will be less likely than patients in private care to receive treatment out of protocol.

The VA has a long history of conducting cooperative surgical trials. Randomization of participants to surgery versus expectant management is not unique to this study. Recent information in the medical and lay press have heightened physician and patient interest in the controversies surrounding treatment of clinically localized prostate cancer. This should assist with participation in our study. This is supported by the fact that so far 45 VAMC's as well as the NCI oncology groups have already agreed to participate.

All procedures, tests and analyses are feasible within the VA and the VA Cooperative Studies Program. The VA Cooperative Studies Program has previously instituted a cooperative study of surgery versus observation for early CAP (VACURG 2). However, this study was of inadequate size to definitively answer the primary study question. Other urologic and surgical VA cooperative studies of similar or greater size to our proposal involving surgery versus expectant management have been conducted. These include subjects with asymptomatic as well as symptomatic disease.

Videotapes and interactive videodiscs have been developed and will be modified to assist with patient education and recruitment for this study. Recruitment of participants will be through veterans organizations, medical and urologic clinics, prostate cancer support groups, NCI newsletters, television, radio and newspaper advertising. The clinical coordinator and Participating Investigator from each center will review the urologic logs, operating room lists, pathology records and cancer registry to identify all patients with CAP who may be eligible for randomization. All eligible patients will be offered randomization. The coordinators will report to the coordinating center a list of four groups: (a) those eligible and randomized; (b) those eligible but not randomized; (c) those eligible but with medical exclusions for which our protocol proscribes entry into the trial and (d) those who do not fulfill our baseline criteria but undergo prostatectomy. A previous surgical trial has utilized this method to ensure adequate enrollment and representativeness of patients (44).

## **XXII. MONITORING THE STUDY**

The groups charged with monitoring the various aspects of the study will be: the Executive Committee, the Data Monitoring Board, the Human Rights Committee, and the Endpoint Committee. These committees will meet at regular intervals according to the prevailing practice of the Cooperative Studies Program.

A. Executive Committee

This committee will consist of the Study Co-Chairmen, the Study Biostatistician, 3-4 Participating Investigators, the director of the central pathology laboratory, and NCI representatives. It is the management and decision-making body for the operational aspects of the study. One of its responsibilities is to monitor the performance of the participating medical centers.

B. Data Monitoring Board

Sixteen members will be nominated including specialists in prostate cancer and four biostatisticians. From these nominations, eight including two statisticians, will be selected to form the DMB. They will review the progress of the study and monitor patient intake, outcomes, and ethical issues. The Board will make recommendations to the Chief of the Cooperative Studies Program and the National Cancer Institute whether the study should continue or be terminated. We suggest that the Data Monitoring Board should consider the following circumstances as grounds for early termination: 1) compelling internal or external evidence of treatment differences, and 2) infeasibility of addressing the study hypothesis (poor adherence, low event rates, poor patient intake). Interim analyses will be provided to the DMB by the Study Biostatistician.

C. Human Rights Committee

This committee will meet every 12 months in conjunction with the Data Monitoring Board to ensure that the patients' rights and safety are being properly protected. In the interim, they may be asked to convene if there is any serious event requiring their attention. They will be presented with a report from the Study Biostatistician as to the progress of the study and ethical issues relevant to the Human Rights Committee.

D. Endpoint Committee

This committee will consist of three independent urologists or experts in prostate cancer and one of the Study Co-Chairmen as a non-voting member. Prior to the start of the study, this committee will establish diagnostic criteria and procedures for endpoint determination. They will review all deaths to make a final determination as to whether or not it was cancer related.

E. Participants-Study Group

Forty-five VA Medical Centers and thirty-five National Cancer Institute centers will be selected to participate. The study group will consist of the Participating Investigators and permanent consultants. They will meet to discuss the progress of the study and any problems encountered during the conduct of the trial. Though this study will not be blinded, overall summaries of study outcomes will not be presented to this group.

F. Monitoring Patient Intake

The intake and operational aspects of this study will be monitored continuously by the Study Co-Chairmen and Study Biostatistician. Participating medical centers will continue in the study only if adequate patient intake is maintained. These actions will only be taken with the concurrence of the Data Monitoring Board or by administrative action of the Central Office.

If recruitment is not proceeding at an appropriate pace, reasons for patient exclusion will be scrutinized by the Co-Chairmen and the Study Biostatistician. Based on this information the Executive Committee may choose, with the approval of the Data Monitoring Board and Cooperative Studies Evaluation Committee, to extend the recruitment period in some or all centers, to add additional centers, or to make minor modifications to the entrance criteria.

G. Monitoring Medical Center Performance

Strict adherence to the protocol will be expected of every participating center and monitored by the Data Monitoring Board, the Executive Committee and the Study Group. A log of all patients with prostate cancer, their reasons for exclusion and inclusion will be collected by the participating centers and reviewed by these committees. Documentation of protocol breaches will be required and the medical centers with repeated protocol violations will be recommended for termination to the Data Monitoring Board. If a Participating Investigator feels that adherence to the protocol will in any way be detrimental to a particular subject's health or well-being, the interest of the patient must take precedence.

By agreeing to participate in the study, the medical center delegates responsibility for global monitoring of the ongoing study to the Cooperative Studies Program committees and personnel listed above. However, the Research and Development and the Human Studies Subcommittees of the medical center

may require Participating Investigator to submit annual and final progress reports concerning the status of the study at the medical center for local monitoring purposes.

### **XXIII. PUBLICATION POLICY**

All publication policies will be decided by the Executive Committee.

The primary publication (s) directly related to the objectives of this Cooperative Study Protocol will be authored by the Study Co-Chairmen, the Study Biostatistician, and, as deemed appropriate by the Executive Committee, other Participating Investigators who have made significant contributions to the writing of the manuscripts. All study participants will be included on the author line as "and the CS407 Study Group."

Acknowledgment must be given on all publications to all participants, members of the Executive Committee, Data Monitoring Board, consultants, supporting personnel of the CSPCC, and the Central Administration of CSP. The statement, "Supported by Cooperative Studies Program Medical Research Service, Department of Veterans Affairs Central Office, Washington, D.C. and the National Cancer Institute, Washington, D.C." must be included in all publications.

Authorship of secondary publications related to the protocol will be decided by the Executive Committee. Data derived from the cooperative study are the property of the Cooperative Study Group, not the property of the individual Participating Investigator or the health care facility where the data were generated. By participating in the cooperative study, participants agree to accept the principle that results from their individual health care facility will be published separately only with the approval of the Executive Committee.

Any publication related to the major endpoints or outcomes during the active phase of the study must have the prior approval of the Data Monitoring Board. All manuscripts are to be approved by the Chief at the Coordinating Center before submission for publication.

### **XXIV. QUALIFICATIONS OF PARTICIPATING CENTERS**

1. There will be a Participating Investigator (PI) at each center. PIs who are not themselves urologists must identify a collaborating urologist at their institution.

2. The urologic surgical team at the participating center should have performed at least 10 radical prostatectomy procedures per year for the previous two years with an operative mortality less than 3%.

3. A staff urologic surgeon must be scrubbed on all study procedures.

4. A pathology department must be willing to provide biopsy and surgical specimens for central reading.

## **XXV. HUMAN RIGHTS CONSIDERATION**

The need for a randomized trial has been recognized before, but always with the caveat that the study would not be ethical because surgery is the generally accepted treatment. The problem with this ethical position is that ineffective or toxic therapies can never be discarded. In a more contemporary formulation, a randomized trial is considered ethical when a state of "clinical equipoise" exists; i.e. when there is sufficient scientific uncertainty to result in honest professional disagreement among expert clinicians, even though any individual may believe one treatment to be clearly superior. The currently available data do not define a superior therapeutic strategy and suggest clinical equipoise. Recent analyses of available data for different therapies in localized prostate cancer have been unable to provide definitive statements on the preferred therapy. They have concluded that a clinical trial comparing prostatectomy versus expectant management is not only ethical but necessary to determine whether prostatectomy improves survival and quality of life in patients with clinically localized prostate cancer compared to expectant management with palliative treatment reserved for symptomatic disease progression.

Theoretically, radical prostatectomy can provide curative therapy for localized CAP. However, radical prostatectomy has perioperative morbidity and mortality. Combined with CAP persistence, recurrence, CAP and non-CAP deaths in the prostatectomy group, these factors may eliminate the benefits of surgery. Expectant management with palliative treatment for symptomatic or metastatic disease progression may be equally effective in patients with localized CAP and not expose them to the risk of surgery or early and toxic adjuvant therapy. However, these patients may develop symptomatic or metastatic disease progression that perhaps could have been prevented from early prostatectomy. The questions exist: is a potentially curative procedure possible in those whom it is necessary and is it necessary in those for whom it is possible? Only a randomized trial as outlined in our proposal will answer these questions.

## **XXVI. BUDGET JUSTIFICATION**

A capitation system is being utilized for reimbursement. Data collection forms, procedures and visits have been simplified to collect only essential information for the main outcome measures.

All patients with prostate cancer will be recorded on monthly prescreening registry logs to enhance enrollment and determine comparative baseline characteristics of enrolled and nonenrolled men with CAP. To ensure timely and complete data collection, each center will receive \$125 per monthly prostate cancer prescreening log completed. Information required for this log is routinely collected and readily available. Therefore, the additional time needed to complete the registry logs should be relatively minor. Total annual reimbursement for completed and submitted monthly logs will therefore equal \$1500.

For each eligible subject on the registry who views the information videotape an additional \$50 up to a maximum of \$5000/center/year will be provided.

A reimbursement of \$1000/patient enrolled will be provided centers. This reimbursement will be necessary to assist in the initial patient evaluation.

The participating investigator will be responsible for 5 visits/patient the first year of enrollment and semiannual visits after that. It is anticipated that many patients will make unscheduled visits for prostate cancer related concerns. Therefore, we will reimburse centers \$400/year for years 1-4; \$450/year for years 5-9 and \$500/year for years 10-15. An additional \$1,000 per center per year is provided in years 1-3 to assist centers in other operating costs (e.g. office supplies, support to the local laboratory for processing sera specimens or the local pathology laboratory for effort in providing tissue biopsy slides).

Therefore the anticipated average annual reimbursement for a center completing the 12 monthly logs, having 75 patients watch the videotape and then randomizing and following 10 participants per year will be: Year 1: \$20,250; Year 2: \$24,250; Year 3: \$28,250. The average reimbursement for centers after recruitment is completed is between \$12-15,000/year.

These funds will be distributed on a quarterly basis to participating centers. An accounting system will be developed at the CSPCC that will count the number of monthly logs, the number of video viewings, and follow-up visit forms submitted, as well as determine the number of patients randomized for a given quarter. The accounting will be based on the first monthly data run after the completion of the quarter for which disbursement will occur.

It is, therefore, incumbent on the participating centers to submit forms in a timely manner. For example, if no forms are submitted to Perry Point in a given quarter, the only reimbursement a center will receive is the randomization allowance (\$1000/patient).

The patient information and educational videotape is critical for participant recruitment. Each center will be provided three copies of the videotapes so that families can "sign them out" and review the videotapes at home if desired. The start-up costs of making the educational videotape are largely covered through other research funds. However, the specifics of our study have been incorporated into this videotape; and therefore, require that a reimbursement above the cost of the videotape be included.

Because of the large number of centers and participants involved and the collaboration of the VA with the NCI, the following administrative support is needed in the Chairman's office:

Dr. Wilt:	Project Administrator (GS-11)
	Project Program Assistant (GS-5) (1/2 time)

The chairman's office will require a FAX machine and two computers for data input, communications, newsletters, etc.

All examinations, therapies, and laboratory tests except those mentioned above, are considered within the context of standard clinical practice and therefore, should be performed at the local centers at no costs to the study.

## **XXVII. JUSTIFICATION OF CENTRAL LABORATORY**

Funding is requested for processing, shipping and central measurement of prostate specific antigen (PSA). This biomarker is a sensitive measure of disease progression. In an attempt to minimize patient crossover due to an asymptomatic rise in PSA, we are blinding PSA and having this measured in a central location. A central laboratory using standardized assay techniques is also necessary to accurately measure



baseline PSA and change in PSA. The central laboratory will notify local centers if a PSA measurement rises to a predetermined "action level." This laboratory will also serve as a serum bank for additional serologic analyses.

Funds are requested for mailing tissue biopsy and prostatectomy specimens. It is critical that a central standardized reading of the specimens is obtained to ensure reliable description of our study population and assess for predictors of all-cause or prostate cancer specific mortality.

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**APPENDIX A**  
**HUMAN RIGHTS REVIEW**  
**AND**  
**INFORMED CONSENT**

May 27, 1993

Joseph Collins, Ph.D.  
Chief, Cooperative Studies  
Coordinating Center  
V.A. Medical Center  
Perry Point, MD. 21902

Dear Dr. Collins:

The Human Rights Committee (HRC) met with the Planning Committee on Tuesday, May 25, 1993, at the Omni Inner Harbor Hotel, in Baltimore, Maryland to review VA Cooperative Study #407: Prostate Cancer Intervention Versus Observation Trial (PIVOT): A randomized trial comparing radical prostatectomy versus palliative expectant management for the treatment of clinically localized prostate cancer.

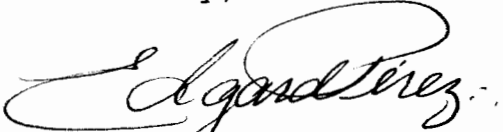
The HRC met with Dr. Collins to discuss and review the aforementioned protocol. Later on, at a joint meeting with the Planning Committee, the Principal Proponents, Drs. Timothy J. Wilt, M.D. and Michael K. Brawer, M.D. gave the HRC an overview and an update of the study.

Afterwards, the HRC Committee reconvened making the following recommendations:

- o Principal proponents to do a complete re-write of the inform consent, beefing up areas not clear, including all verbal recommendations given by the HRC, i.e.; Procedures: Clarify the two types of procedures. As presently written, it gives the impression of 6 different procedures, when in fact there are only two. Procedure 2, 3 & 4 should be 1a, 1b, and 1c.. Procedure # 5 should be #2 and Procedure # 6 should # 3.
- o Page 15 of the protocol Sec. VIII. SECONDARY OBJECTIVES AND ENDPOINTS: Rewrite this paragraph deleting "primary hypothesis" and "aggressive" etc.
- o HRC to receive a copy of the script for the training Video, and at a later date to have the opportunity to view the Video.
- o The purpose of the Video is to ensure the standarization of the training of personnel who will be administering the inform consent. Through this process, study participants will have a consistent interpretation of the purpose of the study.

Once the aforementioned revisions have been made the HRC Committee will meet in a separate meeting to discuss and give our determination for this study.

Sincerely,

A handwritten signature in black ink, appearing to read "Edgard Pérez". The signature is fluid and cursive, with a large initial "E" and a long, sweeping underline.

Edgard Pérez, Member  
Human Rights Committee, CSP

HRC Attendees

Martin Feldbush  
Susan Leviton  
Maurice Moore  
Thomas Hobbins  
Robin Weiss  
Joe Libonati  
Edgard Pérez

July 20, 1993

Joseph Collins, Ph.D.  
Chief, Cooperative Studies  
Coordinating Center  
V.A. Medical Center  
Perry Point, MD 21902

Dear Dr. Collins:

The Human Rights Committee (HRC) met with the Planning Committee on Friday July 16, 1993, at the Omni Inner Harbor Hotel, in Baltimore, Maryland to review VA Cooperative Study #359: "A Clinical Trial Comparing the Safety and Efficacy of Alpha Blockade and Androgen Suppression for the Treatment of Benign Prostatic Hyperplasia".

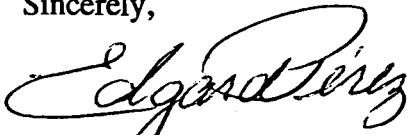
The HRC met with Dr. Collins to discuss and review the aforementioned protocol. Later on, at a joint meeting with the Planning Committee, the Principal Proponent, Dr. Herbert Lepor, MD, gave the HRC an overview and an update of the study.

The randomization of this study is going well, and the use of the drugs has not been problematic.

Additionally we reviewed two revised consent forms for CSP #398 "The Efficacy of Tactile-Thermal Application for Treatment of Dysphagia Resulting from Stroke", and CSP #407 "Prostate Cancer Intervention Versus Observation Trial (PIVOT): A Randomized Trial Comparing Radical Prostatectomy Versus Palliative Expectant Management for the Treatment of Clinically Localized Prostate Cancer".

The revisions of the aforementioned revised consent forms were greatly improved and since the CSP #359 was going well with no human rights issues detrimentally affecting the participants, the Human Rights Committee approved them all.

Sincerely,



Edgard Perez, Member  
Human Rights Committee, CSP

HRC Attenders:

Susan Leviton, Joe Libonati, Maurice Moore, Edgard Perez, and Thomas Hobbins (Via Telephone Conference)





Subject Name: \_\_\_\_\_ Subj # \_\_\_\_\_

Participating Investigator: \_\_\_\_\_ Date:     /     /      
Mo Day Yr

VAMC Name: \_\_\_\_\_ VAMC # \_\_\_\_\_

Title of Study: Prostate Cancer Intervention Versus Observation Trial (PIVOT):  
A Randomized Trial Comparing Radical Prostatectomy Versus Palliative Expectant  
Management for the Treatment of Clinically Localized Prostate Cancer - CSP #407

**DESCRIPTION OF RESEARCH BY INVESTIGATOR**

**PURPOSE:** You have been asked to take part in this research study because you have cancer that is without sign of spread beyond the prostate. The purpose of this study is to find out whether treatment of prostate cancer by immediate surgery to remove the prostate (called radical prostatectomy) and immediate intervention for any reappearance of cancer is better than closely watching, waiting and treating symptoms if and when cancer progresses (called expectant management). Both treatments being given in this study have been used routinely but are now being studied to compare the benefits and effectiveness of each. The study is planned to last a total of 15 years. The following provides a brief explanation about prostate cancer and options that are available for treatment.

Background information about prostate cancer: Cancer of the prostate (CAP) is the most frequently diagnosed nonskin cancer and the second leading cause of cancer related deaths. CAP increases with age, with the most common age at diagnosis of 72 years. There is a high frequency of cancer in the prostate found at autopsy of men who die of other causes. Because of the slow progression rate of the tumor, the age and other medical conditions at diagnosis, men with CAP are more likely to die from some other cause. Other studies have shown that 30% of men over the age of 50 have prostate cancer and that only 1 in 200 men will die directly from prostate cancer. However, if CAP progresses to be detectable by physical exam, death from CAP increases to one in four.

Expectant management in treatment of prostate cancer: Previous studies show that the chances of being alive after 10 years is about the same whether men receive immediate surgical removal of the prostate or expectant management. Because of this, doctors in Europe and Scandinavia generally recommend expectant management. This treatment, however, does not offer the possibility of cure that might result from removal of the prostate. Treatment by expectant management does avoid any of the serious complications including death that can occur at the time of surgery. It is currently used in between

20%-30% of men with prostate cancer that have no sign of spread outside of the prostate. If symptoms develop, they have generally been successfully treated with hormone therapy, surgical procedures that will maintain normal urine flow or local radiation treatment. That is, symptoms can be treated without removing the prostate by radical prostatectomy.

SUBJECT'S IDENTIFICATION (I.D. plate or give name - last, first, middle)



Subject Name: \_\_\_\_\_ Subj # \_\_\_\_\_

Participating Investigator: \_\_\_\_\_ Date: \_\_\_/\_\_\_/\_\_\_  
Mo Day Yr

VAMC Name: \_\_\_\_\_ VAMC # \_\_\_\_\_

Title of Study: Prostate Cancer Intervention Versus Observation Trial (PIVOT):  
A Randomized Trial Comparing Radical Prostatectomy Versus Palliative Expectant  
Management for the Treatment of Clinically Localized Prostate Cancer - CSP #407

**Surgical treatment of CAP:** Surgical treatment of prostate cancer (prostatectomy) involves removing the prostate gland and nearby lymph nodes that may contain cancer. In men with prostate cancer that has not spread out of the prostate gland and who have had a radical prostatectomy, the chances of dying from prostate cancer within 10 years is 15%. In men whose prostate cancer has spread to other organs including lymph nodes, the chances of dying from prostate cancer after 10 years is 85%. Some doctors think that since these chances are so different, that if the cancer is discovered early and removed by surgery before it spreads, a man will be "cured." Surgery is believed to be especially likely to remove the cancer if the prostate cancers are small and slowing growing. However, most of these men would ordinarily die from some cause other than their prostate cancer anyhow. There would be no benefit from surgery but these men would still suffer the risks of surgery. Therefore, these men might do just as well using expectant management.

Surgery is also performed in some men who have prostate cancer that is large or fast growing because these men have a high risk of dying from prostate cancer. However, men with large or fast growing prostate cancer have a high probability that the cancer will reappear even after the prostate is surgically removed. They are unlikely to be "cured" by surgery. Even when the surgeon believes all the cancer has been removed, 40% of these men will have cancer reappear after 10 years. These men will have faced the risks of surgery without the benefit of cure.

Only one study has directly compared the results of men treated with radical prostatectomy with those treated with expectant management. In that small study there was no difference in survival at 15 years between the men treated with prostatectomy or with expectant management.

**Radiation treatment of CAP:** Radiation therapy is also used for treatment of CAP. However, previous studies indicate that men treated with radiation have a higher rate of cancer reappearing than men treated with prostatectomy. Therefore, radiation therapy is generally reserved for men who are poor surgical candidates or have disease beyond the prostate gland. Complications from radiation are similar to prostatectomy and include incontinence, impotence and colostomy. Death due to radiation therapy occurs in less than 0.5% of patients. We have not included radiation therapy as a separate treatment group. Radiation therapy is an option if you decline to enter this study.

**PROCEDURES:** If you agree to take part in this study, you will be assigned by chance to receive either Radical Prostatectomy or Expectant Management.

Subject Name: \_\_\_\_\_ Subj # \_\_\_\_\_

Participating Investigator: \_\_\_\_\_ Date:    /    /     
Mo Day Yr

VAMC Name: \_\_\_\_\_ VAMC # \_\_\_\_\_

Title of Study: Prostate Cancer Intervention Versus Observation Trial (PIVOT):  
A Randomized Trial Comparing Radical Prostatectomy Versus Palliative Expectant  
Management for the Treatment of Clinically Localized Prostate Cancer - CSP #407

**Treatment by Radical Prostatectomy.** If you are assigned to the radical prostatectomy group you could have up to two surgical procedures. You will be hospitalized for a prostatectomy within six weeks. Many surgeons first remove the lymph nodes from near the prostate gland (pelvic lymph node surgery). The pathologist will examine the lymph nodes for cancer cells. Some surgeons, however, do not remove the lymph nodes first and proceed with the prostatectomy as described below. Your surgeon will explain which method he/she uses.

If the lymph nodes do not contain cancer, you will receive a prostatectomy at the time of or within two weeks following the pelvic lymph node surgery. The procedure includes the removal of the entire prostate gland and the pouches that produce the seminal fluid (seminal vesicles) including the part of the urethra that passes through the prostate.

If your lymph nodes do contain cancer, you may not receive a prostatectomy because the cancer has spread outside of your prostate. Your doctor will discuss therapy options with you. These options are all part of current clinical practice and are not considered experimental. In general, they consist of radiation therapy, hormone therapy by pill, removal of the testicles, chemotherapy, mechanical interventions to open blocked passages in your bladder or kidneys, or expectant therapy to await disease progression or symptoms if they should occur.

If your disease returns, is not completely eliminated, or worsens, your doctor will provide you with other treatment options that are considered part of current clinical practice.

**Treatment by Expectant Management.** If you are assigned to the expectant management group you will not receive either a lymph node dissection or radical prostatectomy. Therefore, there will be no attempt to completely remove the cancer. Instead, you will be closely observed in a similar manner to the radical prostatectomy group. If the cancer does not spread to other organs or cause symptoms, no further treatment will be necessary. If the cancer causes symptoms, treatment will be aimed at providing relief of these symptoms. Symptoms that may be due to spread of prostate cancer are: blood in the urine, decrease in urine stream, swelling of the legs, pain in your pelvis, pain in other organs or bones, fatigue. Your doctor will closely examine you to determine if these symptoms are due to prostate cancer. Additionally, treatment will be provided if tests demonstrate that the cancer has spread to the bone or to other organs of the body even if you do not have symptoms. These treatments may consist of mechanical, radiation, hormonal, chemotherapy, or rarely prostatectomy as described above. All of these treatment methods are part of current clinical practice. The primary goal of the expectant management arm is to minimize treatment side effects while providing relief of cancer related symptoms. The expectant management treatment cannot completely remove the cancer nor is it able to cure the cancer.



Subject Name: \_\_\_\_\_ Subj # \_\_\_\_\_

Participating Investigator: \_\_\_\_\_ Date: \_\_\_/\_\_\_/\_\_\_  
Mo Day Yr

VAMC Name: \_\_\_\_\_ VAMC # \_\_\_\_\_

Title of Study: Prostate Cancer Intervention Versus Observation Trial (PIVOT):  
A Randomized Trial Comparing Radical Prostatectomy Versus Palliative Expectant  
Management for the Treatment of Clinically Localized Prostate Cancer - CSP #407

**Study Visits.** If you join the study you will have check-ups by your physician at weeks 6 and 12 following entry, then at six months and every six months for the remainder of the study (15 years total). At these check-ups your physician will look for any evidence of cancer by performing a rectal examination, blood tests (including prostate specific antigen [PSA]) and an annual bone scan. The results of all of these tests will be made available to you if your doctors think further treatment is necessary.

**RISKS AND INCONVENIENCES**

**Radical prostatectomy:** As outlined above, radical prostatectomy offers potential complete removal of prostate cancer. However, it may be neither effective nor necessary. Additionally, there are risks and possible complications to surgery. All men in the radical prostatectomy group will have an operation to remove the pelvic lymph nodes. Possible complications include bleeding, infection, or accumulation of tissue fluid (lymphocele) at the operative site, swelling of the legs and, extremely rarely, death.

Possible complications resulting from surgery to remove the prostate gland for men treated with radical prostatectomy alone are strictures (narrowing) of the bladder and/or urethra (8-14%), loss of bladder control (total urinary incontinence 6-10%, partial incontinence 10-25%), or loss of erection of the penis (impotence). Your doctor will do your surgery in a way that saves the nerves necessary for erection if the tumor can still be completely removed. Removing the tumor has priority over saving the nerves. If your doctor performs the surgery to save nerves for erection the risk of impotence is less than 50%. If your doctor does not use nerve saving surgery to remove your prostate the risk of impotence may be as high as 100%. These complications are usually temporary but may be permanent in 5-25% of men. Injury to the rectum requiring additional surgery to repair or remove occurs in 1-3% of men. Death due to surgery occurs in 1% of men.

**Expectant management:** Expectant management reserves therapy until prostate cancer causes symptoms or spreads to other organs. It also emphasizes treatment primarily directed at relieving the symptoms while minimizing side effects of treatment. Therapy in men in the expectant management group will not be necessary if prostate cancer does not cause symptoms or spread to other organs. Therefore, complications and side effects from treatment should be less in the expectant therapy than the prostatectomy group. However, the expectant therapy strategy does not provide the potential for complete removal of prostate cancer. Treatment reserved for symptoms cannot be guaranteed to always be effective. It is possible that if radical prostatectomy had been performed that CAP would have been completely removed and that you would have lived longer.





Subject Name: \_\_\_\_\_

Participating Investigator: \_\_\_\_\_

Date:     /     /      
Mo Day Yr

VAMC Name: \_\_\_\_\_

VAMC #            

Title of Study: Prostate Cancer Intervention Versus Observation Trial (PIVOT):  
A Randomized Trial Comparing Radical Prostatectomy Versus Palliative Expectant  
Management for the Treatment of Clinically Localized Prostate Cancer - CSP #407

**RESEARCH SUBJECTS' RIGHTS:** I have read or have had read to me all of the above.

Dr. \_\_\_\_\_ has explained the study to me and answered all of my questions. I have been told of the risks or discomforts and possible benefits of the study. I have been told of other choices of treatment available to me.

**I understand that I do not have to take part in this study, and my refusal to participate will involve no penalty or loss of rights to which I am entitled. I may withdraw from this study at any time without penalty or loss of VA or other benefits to which I am entitled.**

The results of this study may be published, but my records will not be revealed unless required by law.

In case there are medical problems or questions, I have been told I can call:

Dr. \_\_\_\_\_ at \_\_\_\_\_ during the day, and

Dr. \_\_\_\_\_ at \_\_\_\_\_ after hours.

If any medical problems occur in connection with this study the VA will provide emergency care.

I understand my rights as a research subject, and I voluntarily consent to participate in this study. I understand what the study is about and how and why it is being done. I will receive a signed copy of this consent form.

\_\_\_\_\_  
Subject's Signature

\_\_\_\_\_  
Date

\_\_\_\_\_  
Signature of Subject's Representative\*

\_\_\_\_\_  
Subject's Representative (print)

\_\_\_\_\_  
Signature of Witness

\_\_\_\_\_  
Witness (print)

\_\_\_\_\_  
Signature of Investigator

\*Only required if subject is not competent.

**APPENDIX B**  
**STUDY BUDGET**  
**POSITION DESCRIPTIONS**

## VA COOPERATIVE STUDY 407

Prostate Cancer Intervention Versus Observation Trial (PIVOT): A Randomized Trial Comparing Radical Prostatectomy Versus Palliative Expectant Management for the Treatment of Clinically Localized Prostate Cancer

STUDY BUDGET

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6	Year 7
Participating VAMC							
Costs for Enrollment:							
12 monthly logs @\$125	1,500	1,500	1,500				
75 pts/yr watching videotape @\$50/patient	3,750	3,750	3,750				
10 patients/yr randomized @\$1,000 ea	10,000	10,000	10,000				
Costs for Follow-up:							
\$400/pt Yr 1 (\$200/visit Yrs 2-5, \$225/visit Yrs 6-10, \$250/visit Yrs 11-15)	4,000	8,000	12,000	12,000	11,520	12,440	11,940
Other Operating Costs	<u>1,000</u>	<u>1,000</u>	<u>1,000</u>	<u>12,000</u>	<u>11,520</u>	<u>12,440</u>	<u>11,940</u>
Total	20,250	24,250	28,250	24,000	23,040	24,880	23,880
Total (45 VA Centers)	911,250	1,091,250	1,271,250	540,000	518,400	559,800	537,300



STUDY BUDGET (Cont.)

	Year 8	Year 9	Year 10	Year 11	Year 12	Year 13	Year 14
Participating VAMC Costs for Enrollment: 12 monthly logs @\$125 75 pts/yr watching videotape @ \$50/patient 10 patients/yr randomized @\$1,000 ea							
Costs for Follow-up: \$400/pt Yr 1 (\$200/visit Yrs 2-5, \$225 /visit Yrs 6-10, \$250/visit Yrs 11-15)							
Other Operating Costs							
Total	11,460	11,000	10,560	11,255	10,815	10,365	9,945
	<u>11,460</u>	<u>11,000</u>	<u>10,560</u>	<u>11,255</u>	<u>10,815</u>	<u>10,365</u>	<u>9,945</u>
Total (45 Centers)	515,700	495,000	475,200	506,475	486,675	466,425	447,525

STUDY BUDGET (Cont.)

	Year 15
Participating VAMC Costs for Enrollment: 12 monthly logs @\$125 75 pts watching videotape @\$50/patient 10 patients/yr randomized @\$1,000 ea Costs for Follow-up: \$400/pt Yr 1 (\$200/visit Yrs 2-5, \$225 /visit Yrs 6-10, \$250/visit Yrs 11-15) Other Operating Costs Total	9,545 <hr/> 9,545
Total (45 Centers)	429,525

Patient Recruitment: 3 years  
 Follow-up: 12 years  
 Participating VA Centers: 45

PROJECT COORDINATOR (GS-11) 1.0 Chairman's Office

**Principal Duties and Responsibilities**

1. The incumbent serves as the Staff Assistant to the Chairman's Office for VA Cooperative Study #407, "Prostate cancer Intervention Versus Observation Trial (PIVOT)". This is a 15 year study in which 80 Medical Centers (45 VAMC and 35 NCI-MC) recruit 2000 patients into the trial. The budget exceeds \$10 million. The Incumbent will serve as contact between the Study Chairman and Perry Point CSPCC the 45 participating VAMC and the 35 NCIMC, working independently most of the time.
2. Major responsibilities include initiation, evaluation, and management of all administrative functions of the Chairman's Office for Cooperative Study #407. Specifically, this involves key responsibilities for overall budget planning and implementation, resource allocation, staff review, preparation and submission of annual budget plan, and position description development for personnel involved in the study.
3. The incumbent serves as principal liaison between the participating stations and the Chairman's Office, the Cooperative Studies Central Offices in Boston and Washington, the Coordinating Center in Perry Point, the Central Pathology Laboratory, the Co-Chairman's Office in Seattle and study group and committee members.
4. The incumbent monitors the performance of study participants as to patient accrual, completeness and timeliness of patient data, and management of funding. He/she recognizes complications in the study and brings them to the attention of the Study Chairman.
5. The incumbent organizes and plans the study meetings of the standing committees and of the study group including selection of dates, development of agenda, coordination of travel plans, and funding requests according to CSP guidelines.
6. The incumbent develops and maintains records of patient accrual, analysis of deaths, and protocol breaches.
7. The incumbent works closely with the Perry Point Coordinating Center and Study Chairman in various analyses of the data.
8. The incumbent reviews all data from the 80 participating centers for completeness and accuracy and makes whatever corrections are necessary in consultation with the appropriate study personnel.
9. The incumbent prepares and meets deadlines for study reports as required by the Perry Point Coordinating Center, the national Cooperative Study Guidelines, the Data Monitoring Board, the Human Rights Committee, and other bodies.
10. The incumbent will be responsible for maintaining patient files containing study forms, appropriate reports and consent forms, on all patients entered into the study, which will number approximately 2000 for this study.
11. The incumbent handles budgetary and logistic aspects of Central Pathology Laboratory relationship with the 80 centers and the Chairman's office and ensures that all specimens are received and read by the Central Laboratory.

12. The incumbent assists the Study Chairman in developing performance standards and job descriptions for research coordinators.

13. The Incumbent is responsible for setting up a contractual arrangement with the three physicians chosen to serve on the endpoints committee. He/she is responsible for sending these individuals reports of death or other endpoints and assuring that they act upon these reports in a timely and complete manner.

14. The Incumbent assists in preparing Cooperative Study Program and any other grant applications, including formulating budget justifications and bibliographies.

#### **Knowledge Required by Position**

1. A thorough working knowledge of the guidelines and regulations associated with the administration of VA-funded research proposals, specifically Cooperative Studies.
2. Thorough knowledge of the Study Protocol, Operations Manual and Research Data Forms for CSP #407. He/she shall understand the objectives of the Study as well as its organization, procedural rules, personnel, material, etc. needed to achieve the Study objectives.
3. Experience in administrative and medical or health-related fields is required.
4. Knowledge and insight is necessary to maintain an accurate data management control system for recording and reviewing all patient data information in order to provide timely information on status and progress of the Study.
5. Knowledge of the administrative functions of the Study Chairman's Office.
6. Knowledge of English grammar, spelling and punctuation to compose error free correspondence and study related manuscripts, abstracts and newsletters.
7. Knowledge to assist in accruing and compiling data statistics for completion of quarterly and annual reports for the Cooperative Study Program. Data needed for reports may have to be extracted from various sources and compiled into a comprehensive format for analysis.
8. Ability to control and balance research funding allotments.
9. Ability to effectively deal with communications of a substantially research/clinical nature from participants and support personnel.
10. The incumbent must demonstrate reliability, independence, and originality in solving problems in the Chairman's absence.

#### **Supervisory Controls**

Authority and responsibility is delegated to the Staff Assistant by the Study Chairman to plan, develop, and direct all activities associated with the professional conduct and successful completion of the Study. The Staff Assistant regularly advises the Study Chairman regarding operating difficulties and other problems associated with the execution of the Study such as lagging patient accrual, breaches of protocol, and patient complications. The incumbent will work with a high degree of independence and completed work is relied on for accuracy.

## PROGRAM ASSISTANT (GS-5) 0.5 Chairman's Office

1. The incumbent serves as the Program Assistant to the Chairman's Office during the three years of participant enrollment for VA Cooperative Study #407, "Prostate cancer Intervention Versus Observation Trial (PIVOT)". This is a 15 year study in which 80 Medical Centers (45 VAMC and 35 NCI-MC) recruit 2000 patients into the trial. The incumbent will assist the Project Coordinator and Chairman in contacts between the Study Chairman and Perry Point CSPCC the participating VAMC and the NCIMC.
2. Major responsibilities include secretarial assistance with all administrative functions of the Chairman's Office for Cooperative Study #407 as defined in the PD for the Project Coordinator. Specifically, this involves telephone contacts, preparation of memos, collecting and monitoring data forms and delivery of laboratory specimens.
3. The incumbent assists the Project Coordinator as a liaison between the participating stations and the Chairman's Office, the Cooperative Studies Central Offices in Boston and Washington, the Coordinating Center in Perry Point, the National Cancer Institute, the Central Pathology Laboratory, the Co-Chairman's Office in Seattle, and study committee members.
4. The incumbent helps the Staff Assistant in monitoring the performance of study participants as to patient accrual, completeness and timeliness of patient data and in preparing Cooperative Study Program and any other grant applications, including formulating budget justifications and bibliographies.
5. The incumbent collects data for the Project Coordinator's review from study centers.

### **Knowledge Required by Position**

1. Experience in word processing and telephone communications is required. Experience in the medical or health-related fields is desired.
2. Experience in maintaining organized study related files and correspondence.
3. Knowledge of the administrative functions of the Staff Assistant to the Chairman.
4. Knowledge of English grammar, spelling and punctuation to compose error free correspondence and study related manuscripts, abstracts and newsletters.

### **Supervisory Controls**

The Program Assistant is directly responsible to the Chairman. However, the incumbent will work closely with the Project Coordinator to coordinate much of the daily duties that are required for successful completion of the study.

### **Personal Contacts**

Establishes and maintains a liaison with various division of the local medical center as well as the Coordinating Center, the participating centers, the Co-Chairman's office, and the Central Pathology Laboratory. The Program Assistant has the ability to maintain effective relationships while maintaining tact, poise, resourcefulness, judgment and the ability to gain cooperation.

### **Physical Demands**

No special physical demands are required to perform the work.



**DEPARTMENT OF VETERANS AFFAIRS**  
**Medical Center**  
**2100 Ridgecrest Drive SE**  
**Albuquerque NM 87108**

**VA COOPERATIVE STUDIES PROGRAM CLINICAL  
RESEARCH PHARMACY COORDINATING CENTER (151-I)**

July 30, 1993

In Reply Refer To: 501/151-I  
CSP #95/#407  
File: C

David G. Weiss, Ph.D.  
CSPCC (151-I)  
VA Medical Center  
Perry Point, MD. 21902

THRU: Chief, CSPCC Perry Point

SUBJ: CSPCRPCC Biopharmaceuticals/Pharmacokinetics Laboratory Materials for CSP #407.

1. Enclosed is the proposed budget for the Albuquerque Biopharmaceutics/Pharmacokinetics Laboratory (BPL) to perform prostate specific antigen analysis (PSA) for CSP #407. "Prostate Cancer Intervention Versus Observation Trial".

2. The budget is based on the assumption that there will be 80 participating sites and the duration of the study will be 15 years. Other assumptions are stated as part of the budget justification.

JAMIE G. BARNHILL, Ph.D  
Chief, Biopharmaceutics/Pharmacokinetics Laboratory  
VA Cooperative Studies Program  
Clinical Research Pharmacy Coordinating Center

CONCUR:

MIKE R. SATHER, M.S., F.A.S.H.P.  
Chief, VA Cooperative Studies Program  
Clinical Research Pharmacy Coordinating Center

Enclosures

**CSPCRPCC BIOPHARMACEUTICS/PHARMACOKINETICS LABORATORY  
ASSUMPTIONS AND JUSTIFICATIONS FOR CSP #407**

1. Blood drawing supplies for participating sites have been included in the budget. These items may be part of the standard supplies found at the clinics.
2. It is assumed that each of the 80 sites will have access to centrifuge for spinning the blood samples for collection of the serum.
3. It is assumed that each participating site will have suitable freezer space to store the serum samples until the time of each monthly shipment. During the year with the greatest number of subjects expected to participate, the average is approximately 7, so the number of tubes requiring storage and the total size of needed storage is very small.
4. It is assumed that each participating site will have access to dry ice for shipment of the serum samples in the insulated mailers.
5. Most supplies have been budgeted to be purchased in large quantities at only a few points in time. Those items that are required to be sterile and those items that are large and require plenty of storage space are budgeted to be purchased at more frequent intervals.
6. All supplies have been calculated with a 4% yearly increase to offset inflation.
7. Insulated mailers have been budgeted for each participating site each month of the study. It is possible to reuse the mailers, however this requires the VA CSPCRPCC to mail the containers back to each location. This would require additional monies to be added to the "Shipping Costs" portion of the budget.
8. Two ultra-low temperature freezers have been requested. One will be located in the warehouse area of the CRPCC and one will be located inside the BPL. Each is equipped with a chart recorder, alarm, racks, and CO<sub>2</sub> backup. The life span of these types of freezers is ten years therefore, funding is requested for two new freezers in year ten. The prices reflect a 4% yearly increase in cost.
9. An Abbot IMX analyzer is requested for performing the PSA assays. Funding is requested again in year eight for the replacement of the analyzer.
10. A computer is requested in year one for data handling and tracking.
11. Funds have been requested to offset maintenance, service and repair on the freezers and analyzer.
12. A GS-8 chemist/technician is requested. The duties of this individual will include (but are not limited to) conducting the PSA assays, performing the routine maintenance and calibration on the equipment, maintaining the data, coordinating the arrival, transfer and log-in of samples, and preparing the data reports.
13. The budget is calculated assuming the PSA kits will be donated. The purchase price to the VA for each PSA kit would be \$656. The total cost for the kits, should they have to be purchased, is indicated under the section, "SUPPLIES - Assay."

**CSPCRPCC BIOPHARMACEUTICS/PHARMACOKINETICS LABORATORY  
SAMPLE HANDLING PROTOCOL FOR CSP #407**

Blood samples will be obtained by venipuncture using vacuum redtop tubes. The sample should be allowed to coagulate and is then spun in a centrifuge to separate the serum from the clot. The stopper should then be gently removed and two 2ml aliquots should be pipetted into labeled storage tubes. The tubes should then be frozen until the time of shipping. Storage tubes, labels, and disposable pipettes will be provided.

Once monthly, or more frequently if necessary, all samples should be gathered together, placed into the insulated mailer, surrounded by dry ice, carefully sealed, and shipped to the VA CSPCRPCC by overnight mail.

At the CRPCC, the packages will be checked, logged-in, and the contents will be placed into one of the ultra-low temperature freezers. At weekly intervals, the duplicate samples will be separated and one portion will be transported to the Biopharmaceutics/Pharmacokinetics Laboratory (BPL) on ice.

At the BPL, the samples will be logged-in, issued a chain-of-custody document, and placed into the appropriate location in an ultra-low temperature freezer.

At period intervals, the subjects serum will be removed for determination of PSA levels. At that time, the samples will be brought to room temperature and gently mixed. Duplicate 150 ul aliquots will be tested.



CSPCRPC BIOPHARMACEUTICS/PHARMACOKINETICS LABORATORY  
 BUDGET FOR CSP# 407  
 AUGUST 2, 1993

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6	Year 7	Year 8	Year 9	Year 10	Year 11	Year 12	Year 13	Year 14	Year 15	TOTAL
<b>PERSONNEL</b>																
Technician/Chemist	31,449	33,797	34,283	34,915	40,094	43,366	45,101	48,285	50,216	51,652	53,717	55,866	62,104	64,588	67,171	722,604
GS-4 (1.0 FTR)																
Includes 25% Fringe Benefits																
<b>SUPPLIES</b>																
Blood Drawings																
1. Red-top Tubes	1,770	2,110	1,644	1,736	1,644	1,644	1,736	1,644	1,609	1,609	1,741	1,569	1,569	1,569	543	12,726
2. Needles	1,248	1,516	1,311	1,242	1,242	1,242	1,242	1,242	1,343	1,343	1,055	1,073	1,073	1,073	311	9,189
3. Holders	339	370	370	404	404	404	404	404	471	471	471	471	471	471	471	2,112
4. Swabs	384	322	322	265	265	265	265	265	298	298	298	298	298	298	298	1,229
5. Tourniquets	1,650	1,650	1,650	1,650	1,650	1,650	1,650	1,650	1,650	1,650	1,650	1,650	1,650	1,650	1,650	3,200
6. Band-Aids	1,020	1,020	1,020	1,020	1,020	1,020	1,020	1,020	1,020	1,020	1,020	1,020	1,020	1,020	1,020	3,270
<b>Sample Handling</b>																
1. Disposable Pipettes	644	575	575	575	575	575	575	575	575	575	575	575	575	575	575	2,799
2. Sample Storage Tubes	4,930	4,400	4,400	4,400	4,400	4,400	4,400	4,400	4,400	4,400	4,400	4,400	4,400	4,400	4,400	21,081
3. Tube Labels	800	800	800	800	800	800	800	800	800	800	800	800	800	800	800	2,400
<b>Assay</b>																
1. Pipette Tips	600	720	720	720	720	720	720	720	720	720	720	720	720	720	720	1,920
2. Calibration and Control Samples and Diluter	630	643	671	671	725	754	784	815	848	882	917	954	992	1,032	1,073	12,409
3. <PRA Kit>	<49,856>	<57,072>	<53,792>	<51,168>	<48,544>	<46,376>	<44,208>	<42,040>	<40,016>	<38,048>	<36,080>	<34,112>	<32,144>	<30,176>	<28,208>	<723,568>
<b>Protein Storage</b>																
1. Divided Beams	1,756	190	190	190	190	190	190	190	190	190	190	190	190	190	190	3,512
2. Recorder Charts	190	190	190	190	190	190	190	190	190	190	190	190	190	190	190	950
<b>Shipping Costs</b>																
1. Insulated Mailbox	6,912	7,188	7,476	7,775	8,064	8,410	8,746	9,095	9,459	9,837	10,230	10,640	11,065	11,508	11,987	138,394
2. Overnight @ \$10/pkg and once monthly shipments	9,600	9,600	9,600	9,600	9,600	9,600	9,600	9,600	9,600	9,600	9,600	9,600	9,600	9,600	9,600	144,000
<b>EQUIPMENT</b>																
1. Ultra-Low Temp. Freezers (2) with alarms, encoders, racks, and CO2 backup	21,840															62,640
2. Abbott BDX Analyzer	48,000							48,000								96,000
3. Computer	2,500															2,500
4. Service/Installation/Upgrade	1,000	1,000	1,000	1,000	1,000	1,000	1,000	1,000	1,000	1,000	1,000	1,000	1,000	1,000	1,000	15,000
<b>TOTAL</b>	141,312	53,230	58,656	64,609	63,958	74,394	74,394	116,795	74,075	119,159	79,066	78,066	92,903	87,728	91,755	1,235,655

<> Not included in total.

**APPENDIX C**  
**CURRICULA VITAE**

**CURRICULUM VITAE**  
**Timothy James Wilt, M.D., M.P.H.**

**Personal Data:** Section of General Medicine Minneapolis VA Medical Center/1110  
 One Veterans Drive Minneapolis, Minnesota 55417  
 (612) 725-2000 ext. 2681 Fax: (612) 725-2118

**Education:** 1974-1978 The Colorado College, Colorado Springs, CO - B.A. Chemistry  
 1978-1983 University of Illinois College of Medicine - M.D.

**Postgraduate Training:** 1983-1986 Internship and Residency in Medicine,  
 University of Minnesota, Minneapolis, MN  
 1987-1990 Masters in Public-Health, University of Minnesota,  
 Graduate School of Public Health

**Academic Positions:** 1986-1987 Chief Medical Resident, Minneapolis VAMC Minneapolis, MN  
 1987-1990 Clinical Instructor University of Minnesota, MVAMC  
 1990 Assistant Professor of Internal Medicine  
 University of Minnesota, MVAMC, Minneapolis, MN

**Honors:** 1979 College of Medicine Summer Research Fellowship  
 1979-83 James Scholar Program for Independent Study in Medicine  
 1981 Bertram Richardson Scholarship for Overseas Studies  
 1982 Richard Muldavsky Scholarship for Excellence in Physiology  
 1983 Medical Student Research Forum First Place Award  
 1986-87 Chief Medical Resident, MVAMC, Minneapolis, Minnesota

**Board Certification:** 1986 American Board of Internal Medicine

**Licensure:** 1984 - State of Minnesota #029677 5

**Professional Organizations:** Phi Beta Kappa; American Chemical Society; American College of  
 Physicians; Society for General Internal Medicine

**Teaching/Administrative Positions:** \* Chief Medical Resident, Minneapolis VAMC (1986-87)  
 \* Director Admissions Area, MVAMC (1987-90)  
 \* Co-director General Medicine Walk-in Clinic, MVAMC (1987-90)  
 \* Director General Internal Medicine Fellowship Program (1989-present)  
 \* Director Medical Preoperative Clinic (1989-92)  
 \* Director Medicine Residents Ambulatory Care Rotation (1989-92)  
 \* Member: Professional Standards Board MVAMC 1991-92  
 \* Staff Physician General Medicine Section; MVAMC

**Research: Epidemiology and Prevention of Chronic Diseases**

- \* Co-principal Investigator: Minneapolis Center; Multicenter Isradipine/Diuretic Atherosclerosis Study.
- \* Principle Investigator: Peripheral Vascular Disease in patients in MIDAS.
- \* Co-Investigator: Cholesterol and Recurrent Events (CARE).
- \* Principal Investigator: Peripheral Vascular Disease in the CARE Study.
- \* Principal Investigator: MVAMC site VA Cooperative Study #363: HDL Intervention Trial (HIT).
- \* Principal Investigator: Peripheral Vascular Disease in the HDL Intervention Trial (HIT).
- \* Co-principal Investigator/Project Director: NHLBI-RFP. Arterial Diseases Multi-Intervention Trial.
- \* Chairman: VA Cooperative Study #407. Prostate Cancer Intervention versus Observation trial (PIVOT).

**Previous Grants:**

- Minnesota Medical Foundation: Effect of Fish Oil on hypercholesterolemic men. Co-principal Investigator; \$7900 (1987-88).
- Program grant for Fellowships in Ambulatory Care. Department of Veterans Affairs funded: Program Director: \$120,000 (1990-92)

**Active Grants:**

- Multicenter Isradipine Diuretic and Atherosclerosis Study (MIDAS). Co-Investigator: \$3,000,000 (1989-94) Sandoz Corporation.
- Peripheral Arterial Disease MIDAS. Principal Investigator: \$25,000 (1990-94) Sandoz.
- Program grant for Fellowships in Ambulatory Care. Program Director: \$240,000 (1992-6) Department of Veterans Affairs.
- High Density Lipoprotein Intervention Trial (HIT):VA Cooperative Trial #363. Principal Investigator Minneapolis Site; \$500,000 (1991-98) VA Cooperative Studies Program.
- Ultrasound detection and evaluation of peripheral vascular disease in the HDL Intervention Trial: Principal Proponent; \$117,000 (1992-98). VA Cooperative Studies Program.
- Peripheral Arterial Disease: A pilot study to evaluate treatment and prevention strategies for atherosclerotic cardiovascular disease. Co-principal Investigator/project director; Minnesota site award: \$666,202. (1992-1995) NIH (RFP# NHLBI-HC-92-11).
- Program grant for Education in Primary Care; Fellowship Program director. \$40,000 (1992-96). University of Minnesota Health Right Foundation.
- Observation versus prostatectomy for clinically localized carcinoma of the prostate. VA Cooperative Study #407. Approved for planning. Study Chairman. (1992-93) VA Cooperative Studies Program
- Detection and monitoring of femoral arterial plaque in the Cholesterol And Recurrent Events Study (CARE). Principal Investigator. \$97,800. (1993-96) Bristol Myer-Squibb

**Grants Submitted and Pending Approval:**

- Prostate Cancer Intervention Versus Observation Trial (PIVOT). VA/NCI Cooperative Study #407. (1993-2008)

## **BIBLIOGRAPHY: Published Articles and Books**

- 1) Wilt TJ, Lofgren RP, Nichol KL, Schorer AE, Crespín L, Downes D, Eckfeldt J. Fish Oil Supplementation Does Not Lower Plasma Cholesterol in Men with Hypercholesterolemia: Results of a randomized double blind controlled cross-over study. *Annals Int Med* 1989;111:900-905
- 2) The MIDAS Research Group. Multicenter Isradipine Diuretic Atherosclerosis Study (MIDAS): Design Features. *Am J Med* 1989;86:(4A)37-39.
- 3) Wilt TJ, Lofgren RP, Nichol KL, Eckfeldt J. Fish oil supplements do not treat hypercholesterolemia in middle aged men: *Cardiology Board Review*. 1991;8:80-89.
- 4) Wilt TJ and Cutler A. Physician Performance and Patient Perceptions during the Rectal Examination. *J Gen Int Med* 1991;6:514-517.
- 5) Sacks FM, Pfeffer MA, Moye L, et al for the CARE Investigators. Rationale and Design of a Secondary Prevention Trial of Lowering Normal Plasma Cholesterol Levels after Acute Myocardial Infarction: The Cholesterol and Recurrent Events Trial (CARE). *Am J Cardiol* 1991;68:1436-1446.
- 6) Wilt TJ. Evaluation and Management of Patients with Lower Extremity Peripheral Vascular Disease. *J Gen Int Med* 1992;7:87-101.
- 7) Rubins HB, Schectman G, Wilt TJ, Iwane M., Distribution of lipid phenotypes in Community-Living Men with Coronary Heart Disease. *Archives Int Med* 1992; 152:2412-2416.
- 8) Rubins HB, Robins SJ, Iwane MK, et al. Rationale and Design of the Department of Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial (HIT) for Secondary Prevention of Coronary Artery Disease in Men with Low High-Density Lipoprotein Cholesterol and Desirable Low-Density Lipoprotein Cholesterol. *Am J Card* 1993; 71:45-52.
- 9) Lofgren RP, Wilt TJ, Nichol KL, Crespín L, Pluhar R, Eckfeldt J. Effect of fish oil supplementation on blood pressure: Results of a randomized cross-over trial. *Am J Pub Health* 1993; 83:267-269.
- 10) Wilt TJ. Current Approaches to the Patient with Peripheral Vascular Disease. *Today in Medicine*. 1993;8:21-23.
- 11) Wilt TJ, Sprinkle J, Hass A, Heurer C, Applegate W, Schnaper H, Flack J, Borhani N and Grimm R. Prevalence and Correlates of Peripheral Vascular Disease in hypertensive patients with carotid atherosclerosis: Baseline results from the Multicenter Isradipine/Diuretic Atherosclerosis Study (MIDAS) *J Vasc Med and Bio*. 1993 in press.

## **Letters**

Wilt TJ, Lofgren RP, Nichol KL. Fish Oil Supplementation and Plasma Cholesterol: The Power of a Clinical Trial. *Ann Intern Med*. 1990; 112: 633-4.

Wilt TJ, Ensrud KE, Joseph AM. Milking the Prostate. *JAMA*. 1992; 268:3198-3199.

### **Articles submitted for publication**

Wilt TJ and Macpherson DS. Effectiveness of a medical preoperative clinic in a university affiliated medical center. (Submitted 1993).

Wilt TJ, Brawer MK Barry MJ et al. Clinical trials for localized prostate cancer are ethical, necessary and ongoing. (Submitted 1993).

Wilt TJ, Sacks F, Meyers D and Davis B. Prevalence and determinants of peripheral vascular disease in the CARE study. (Manuscript in preparation)

Nash DT, Davis B, Wilt TJ and Sacks F. Interrelationships between risk factors at Baseline of the CARE study. (Manuscript in preparation)

### **Invited Lectures**

Wilt TJ. Evaluation and Management of Peripheral Vascular Disease. MVAMC. July 1990.

Wilt TJ. Current Approaches to Patients with Peripheral Vascular Disease. United Medical Center, St. Paul, MN. August 1990.

Wilt TJ. Controversies in Performing the rectal examination. MVAMC. February 1991.

Wilt TJ. Medical Consequences of High Latitude and Altitude Travel. MVAMC, Mpls, MN. July 1991.

Wilt TJ. Screening for Carcinoma of the Prostate. MVAMC. Mpls, MN. December 1992.

Wilt TJ. Is their evidence to support early detection and Treatment of Prostate Cancer. United Medical Center, St. Paul, MN. March 1993.

### **Previous Fellows under Supervision of Dr. Wilt:**

1. Dr. William Conroy. Staff Physician, Park Nicollet Medical Center, Minneapolis, MN.
2. Dr. Jane Pederson. Ambulatory Care and Health Services Research Fellow, MVAMC.
3. Dr. Maureen Murdoch. General Internal Medicine and Epidemiology Fellow, MVAMC.
4. Dr. Christopher Goerd. Ambulatory Care and Epidemiology Fellow, MVAMC.
5. Dr. Cheryl Oncken. General Internal Medicine and Epidemiology Fellow, MVAMC.

## CURRICULUM VITA

MICHAEL K. BRAWER, M.D.  
Chief, Section of Urology  
VA Medical Center  
Seattle, WA

**Education:** B.S. University of California, Los Angeles, CA, 1975  
M.D. University of California, School of Medicine, Los Angeles, CA, Medicine, 1979

### Professional

**Experience:** 1991-Present Associate Professor, Urology, University of Washington, Seattle, WA  
Adjunct Associate Professor, Pathology, University of Washington, Seattle, WA  
1989-Present Chief, Section of Urology, Seattle Veterans Administration Medical Center, Seattle, WA  
1989-1991 Assistant Professor, Urology; Adjunct Assistant Professor, Pathology, University of Washington, Seattle, WA.  
1986-1989 Assistant Professor of Surgery (Urology), University of Arizona Health Sciences Center  
Staff Physician Surgery (Urology), Tucson Veterans Administration Medical Center, Tucson, AZ  
1985-1986 Chief Resident, Department of Surgery, Division of Urology, Stanford University School of Medicine, Stanford, CA  
1981-1982 Resident, Department of Surgery, Stanford University School of Medicine, Stanford, CA  
1980-1981 Intern, Department of Surgery, Stanford University School of Medicine, Stanford, CA

### Publications:

Andriole, G.L., Brawer, M.K., Gerber, G.S. and Mettlin, C.: Prostate cancer screening. *Cortland, Forum*, 12/1992.

Brawer, M.K.: Prostatic Intraepithelial Neoplasia: A Premalignant Lesion. *J. of Cellular Biochemistry*, 16G:171-174, 1992.

Brawer, M.K., Ploch, N.R. and Bigler, S.A.: Prostate cancer tumor location as predicted by needle biopsy. *J. of Cellular Biochemistry*, 7/1992.

Brawer, M.K. Bigler, S.A. and Deering, R.E.: Quantitative morphometric analysis of the microcirculation in prostate carcinoma. *J. of Cellular Biochemistry*, 7/1992.

Brawer, M.K.: Relevance of PSA Continues to Unfold. In: Contemporary Urology 8/1992.

## **CURRICULUM VITA (Cont.)**

**MICHAEL K. BRAWER, M.D.**

### **Publications (Cont.):**

Brawer, M.K.: Prostatic Intraepithelial neoplasia: a premalignant lesion. *Hu. Path.*, 23:242-248, 1992.

Flam, T.A., Brawer, M.K., Cooper, E.H. and Nasser, J.: Diagnosis and markers in prostate cancer. *Cancer*, 70:357-358, 1992.

Brawer, M.K., Chetner, M.P., Beatle, J., Buchner, D.M., Vessella, R.L. and Lange, P.H.: Screening for prostatic carcinoma with prostate specific antigen. *J. Urol*, 147:841-45, 1992.

Pajouh, M.S., Nagle, R.B., Breathnach, R., Finch, J.S., Brawer, M.K. and Bowden, G.T.: Expression of metalloproteinase genes in human prostate cancer. *J. Cancer Res. Clin. Oncol.*, 117:144-150, 1991.

Petein, M., Michel, M. van Velthoven, R., Pasteels, J., Brawer, M.K., Davis, J.R., Nagle, R.B. and Kiss, R. Morphonuclear relationship between prostatic intraepithelial neoplasia (PIN) and cancers as assessed by digital cell image analysis. *Am. J. Clin. Path.* 96:628, 1991.

Sohlberg, O.E., Chetner, M.P., Ploch, N. and Brawer, M.K. Prostatic abscess after transrectal ultrasound-guided biopsy. *J. Urol* 146:420, 1991.

Brawer, M.K., Bigler, S.A., Sohlberg, O.E., Nagle, M.D. and Lange, P.H. Significance of prostatic intraepithelial neoplasia on prostate needle biopsy. *Urol.* 38:103, 1991.

Nagle, R.B., Brawer, M.K., Kittelson, J. and Clark, V. Phenotypic relationship of prostatic dysplasia (intraepithelial neoplasia) to invasive carcinoma. *Am. J. Pathology* 138:119, 1991.

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## CURRICULUM VITA

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### Publications:

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DAVID G. WEISS, Ph.D.

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### Other

**Experience:** Study Biostatistician for planning and/or analysis of the following VA Cooperative Studies:

- CS# 17            VA Cooperative Study on Aphasia: A Comparison of Individual and Group Therapy.
- CS# 59            Patient Compliance and its Role in Dental Plaque Control.
- CS# 85            Antabuse in the Treatment of Alcoholics on Methadone Maintenance.
- CS#110           A Comparison of Hospital and Home Treatment Programs for Aphasic Patients.
- CS#167           Asymptomatic Carotid Stenosis - Etiological Importance in Development of Stroke.
- CS#271           Long-Term Follow-Up of WW-II and Korean Conflict Prisoners-of-War.
- CS#292           Therapy of Primary Amyloidosis (AL).
- CS#309           The Role of Carotid Endarterectomy in Preventing Stroke from Symptomatic Carotid Stenosis.
- CS#328           The Molecular Genetics of Psychiatric Disorders.
- CS#352           Colchicine in the Treatment of Cirrhosis of the Liver
- CS#366           Psychiatric Genetic Linkage
- CS#380           Prospective Evaluation of Risk Factors for Large ( $\geq 1$  cm) Colonic Adenomas in Asymptomatic Subjects
- CS#391           Effect of Polyunsaturated Lecithin on Liver Fibrosis
- CS#407           Prostate Cancer Intervention Versus Observation Trial (PIVOT): A Randomized Trial Comparing Radical Prostatectomy Versus Palliative Expectant Management for the Treatment of Clinically Localized Prostate Cancer

**APPENDIX D**

**NCI LETTER**



## MEMORANDUM

National Institutes of Health  
National Cancer Institute  
Bethesda, Maryland 20892

**To:** Timothy J. Wilt, MD, MPH

**From:** Richard S. Kaplan, <sup>RSK</sup>MD, Senior Investigator, CIB, CTEP, NCI

**Date:** 29 July 1993

**Subject:** PIVOT (Prostate cancer Intervention Versus Observation Trial)

I wanted to summarize for you and for the Dept. of Veterans Affairs Cooperative Studies Program (CSP) the position of support of the Cancer Therapy Evaluation Program of NCI for the PIVOT trial, and how our Cooperative Clinical Trials Groups and other clinical investigators will participate.

First of all, let me reiterate that the scientific rationale for this protocol is viewed as having the highest possible priority to our clinical trials program in prostate cancer. The issues to be addressed in this study have profound implications for most of the other trials under way or planned for early stages of the disease, as well as having critical implications for public health and health care policy. Moreover, the publicity surrounding recent data presentations gives us a window of opportunity of which we need to take advantage to perform what is clearly a most challenging clinical trial.

The challenging part, of course, is to test the strong biases that have long determined patterns of referral and care for prostate cancer patients and this, coupled with the required scale of the trial is such that it would be impossible to mount in our Cooperative Groups alone since they depend substantially on accrual from academic and other referral practices. On the other hand, it might also not be feasible in the Department of Veteran Affairs either without substantial accrual assistance from the Cooperative Group system.

CTEP staff therefore have extensively discussed the protocol, and its importance, with the Group Chairmen and the GU or prostate chairs of all the adult Cooperative Groups and emphasized the priority that we are requesting for this trial within their strategic plans. We are also taking care that major Cooperative Group protocols that would compete for accrual with PIVOT will incorporate eligibility criteria or be prioritized such that eligible patients will be offered the PIVOT trial first.

The next steps for CTEP are to formalize commitment from one or several of our Groups and then to establish commitment of particular member institutions. I will be presenting the protocol in detail at the major Fall full meetings of SWOG, ECOG, NCCTG and CALGB, each of which has expressed substantial interest. From these resources, we anticipate identifying at least 30-40 centers (hopefully more) who will be major participants. We are currently figuring on enrolling about 8 patients per center per year (out of perhaps 50 /year eligible and screened) over 3 years of accrual at each non-DVA center.

Data management and statistical support will be from the DVA Cooperative Studies Program and

without cost to NCI, though it seems to us that the most efficient and reliable strategy would be to have the Groups collect the data in their own Ops/Stat Offices, using a format compatible with that of the DVA-CSP and then forward them. This plan will have the advantage of utilizing the established methods of data quality assurance. However, substantial work may need to be done to develop a common data format. As soon as the CTEP Groups are formally committed (via their committee structures) it will be critical to have personnel from their respective ops/stat offices meet with DVA-CSP staff to coordinate methods of data collection.

Which of course brings us to the question of costs. There will clearly be a need for some cost supplement to the Cooperative Group op/stat offices. For the participating Group members, a substantial portion of the costs will be offset according to their routine Group reimbursement formulas but there is no question that PIVOT will be a personnel-intensive undertaking with some special requirements, and the VA is apparently not in a position to supplement Group members for their participation. Since this trial is every bit as important to DCT as it is to the VA, CTEP is going to find funds to help make it possible for Group members to take on the additional costs of case-finding and what is expected to be a very time-consuming process of acquiring informed consent. We will also push to have PIVOT made an NCI-designated High Priority Trial, which will make additional funds available as well as augmenting its visibility.

Dr. Friedman is confident that CTEP can deliver the support necessary to assure enthusiastic participation in the PIVOT trial by a substantial proportion of its GU investigators and help to assure completion of this key study. He and I are also enthusiastic about the precedent for inter-agency clinical trials of major importance and impact.

cc: Dr. Friedman  
Dr. Ungerleider



**VA COOPERATIVE STUDY 407**

**"PROSTATE CANCER INTERVENTION VERSUS OBSERVATION TRIAL (PIVOT):  
A RANDOMIZED TRIAL COMPARING RADICAL PROSTATECTOMY VERSUS  
PALLIATIVE EXPECTANT MANAGEMENT FOR THE TREATMENT OF  
CLINICALLY LOCALIZED PROSTATE CANCER"**

**VOLUME II  
SUPPORTING INFORMATION**

**- PRIVILEGED AND CONFIDENTIAL -**

Not to be Disseminated Beyond its Official

Committee Function and Use

REVISED OCTOBER, 1994

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**APPENDIX E**  
**BIostatistical AND RESEARCH DATA PROCESSING**  
**(BRDP)**

## **BIOSTATISTICAL AND RESEARCH DATA PROCESSING (BRLP)**

### **I. DATA MANAGEMENT**

This study will be a prospective, randomized trial of two therapeutic management approaches for localized cancer of the prostate (CAP). The two treatment approaches are radical prostatectomy (RP) with aggressive follow-up treatment and expectant management (EM) with palliative symptomatic treatment only. Patients meeting the general inclusion/exclusion criteria for the study will be randomized (by telephone call to the CSPCC at Perry Point) to one of the two management approaches and followed until death or the completion of study follow-up. The trial is planned for 15 years which includes a three-year intake period and a 2-year follow-up beyond the last randomization. Data to be collected at entry includes: patient profile (age, race, family history of CAP activities of daily living (ADL); health status questionnaire with prostatic specific items; complete medical history (with Charlson Score); and, clinical staging information (T,N,MM stage, size by DRE, Gleason grade, and histologic grade). For patients assigned to the radical prostatectomy arm, surgical information will be recorded that includes pelvic lymph node dissection, descriptive characteristics of the prostatectomy procedures, pathologic staging, and surgical complications. Follow-up visits will be scheduled for all patients at six weeks (one month post-op for surgical group), 3, 6, 9, 12 months and every 6 months thereafter until completion of the study. Data to be collected at routine follow-up visits includes: symptom report; pain report; ADL report; bone scan (annually), CAP status and treatment report; clinical staging; tumor size by DRE; and, the quality-of-life/health status questionnaire (annually). In addition, all episodes of CAP treatment will be reported as it is provided on a special treatment summary forms. PSA will be evaluated centrally to monitor for safety and results will be reported directly to the CSPCC. PSA results will be returned to the sites. Biopsy samples from the RP group will be submitted for central review and histopathologic staging and grading. Complete documentation will be required on each death including a narrative summary from the Participating Investigator, hospital discharge summary with clinical chart, autopsy report and/or copy of death certificate. This documentation will be blinded for treatment group and submitted to the Endpoint Committee for adjudication.

At each participating site, data collection will be carried out under the direction of the PI. Data will be recorded on specially developed study data forms (see Volume II, Study Forms). The final responsibility for the completeness and accuracy of all study data at a study center belongs to the Participating Investigator who will review all study forms and affix his signature to each form prior to submitting the forms to the CSPCC (Perry Point). Study forms will be printed on three-part NCR (noncarbon reproducing) paper. The original or top sheet will be submitted to the CSPCC, while the second sheet will be submitted to the Study Chairman's office. The only exception to this will be the informed consent documents where the originals will be kept at the participating center and copies submitted to the CSPCC and Study Chairman's office. A special data form has been developed for the PSA test that will be completed centrally. The CSPCC will be sent the top sheet with the second sent to the Study Chairman's office and the bottom copy retained at the central lab. Results of these tests will not be returned to the local study center, but will be sent directly to the Study Chairman's office and the CSPCC. Separate from the study forms, each study patient death will be reported to the Study Chairman's office (with copies to the CSPCC) by the Participating Investigator in a narrative summary detailing the circumstances including cause, autopsy reports, copies of patient's chart, etc.

Study data forms received at the CSPCC will be processed at regular intervals (monthly). Data processing will consist of keyentering and keyverifying by study assistants directly into the computer. All data will be extensively computer edited with specially developed editing programs for the purpose of identifying errors such as missing data, values which are outside range limits, and consistency checks prior to entering the study master file. Possible data errors so identified by the edits will be listed on a computer printout and returned to the participating centers for correction and/or confirmation and resubmission to the CSPCC. Overall data flow will be monitored by the Study Biostatistician with special computer software that will summarize missing or delinquent forms as well as provide different measures of data accuracy. Monitoring will also include random checks comparing values in the study masterfile with those on the corresponding data form.

The data flow system described above will result in an updated study masterfile being available at any point in time. Periodic reports will be prepared and provided to the Study Group, Executive Committee, and Data Monitoring Board while the study is ongoing. These are currently planned for approximately six-month intervals to coincide with the annual study meetings and with

additional monitoring reports in between (current meeting schedule: start-up, nine months, annually thereafter). The content of these reports will be described in the sections to follow. A diagram of the data flow for this study appears in Figure 1.

## **II. INTERIM MONITORING REPORTS TO THE STUDY EXECUTIVE COMMITTEE**

### **A. Patient Screening and Enrollment**

During the patient enrollment period, it will be necessary to monitor whether or not enrollment targets are being met. Patient screening information will be recorded on Form 1 which provides a check list of the study inclusion/exclusion criteria. The screening data summaries will be presented in a number of different formats. The monthly screening record will be presented as in Table 1 (example tables appear on pages 99-106). This table will provide both separately, for each month, and cumulatively the numbers of patients screened and rejected along with associated percentages for rejection rates and enrollment rates with respect to projected targets. Table 1 will be provided for all centers combined and separately for each center. The cumulative number of patients enrolled as a percentage of expected will be provided graphically as in Figure 2. Cumulative screening summaries for all patients will be listed by study center as in Table 2. In order to evaluate which screening criteria most affect patient intake, a summary of the reasons for exclusion will be provided as in Table 3, for all centers combined.

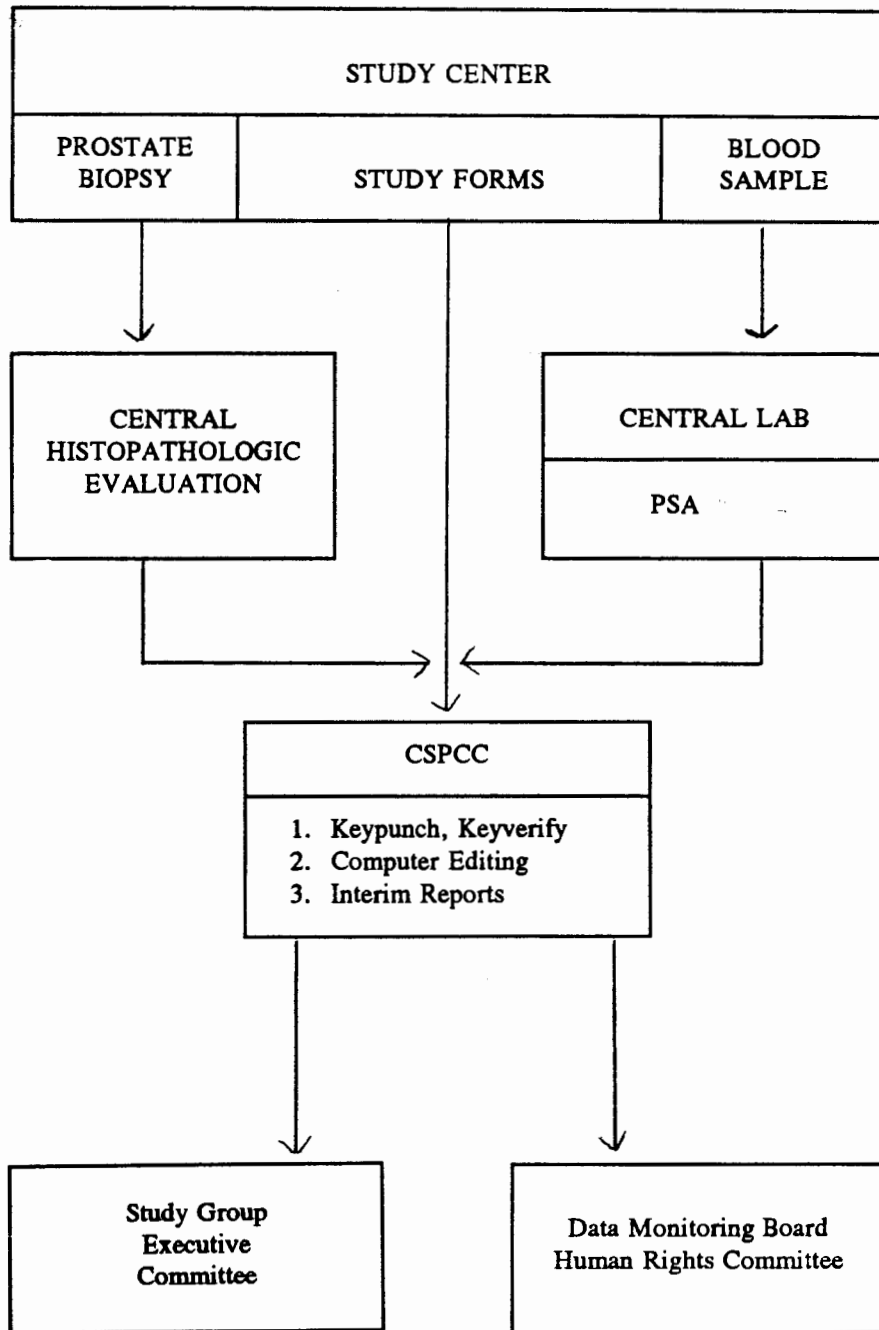
### **B. Study Patient Characteristics at Entry**

The Executive Committee and Study Group report will include descriptive statistical summaries characterizing study patients at entry. Background information will be recorded on study Form 2 and includes demographic measures such as age, race, family history of CAP, performance status, smoking history, medical history (Charlson Score), laboratory data and clinical staging. Race, performance status, family history, medical history and clinical staging will be recorded as categorical variables while age, and laboratory data will be recorded as continuous response variables. Descriptive summaries for categorical variables will be frequencies with percentages and treatment groups will be compared by chi-square procedures; continuous variables will be summarized by means and standard deviations and treatment group comparisons will be by analysis of variance. Background data summaries will be presented as in Table 4 where age (continuous) and



FIGURE 1

DATA FLOW



race (categorical) appear as examples. In addition, laboratory data for each variable will be classified as abnormal/normal and will be summarized as a categorical variable with frequency of abnormal values appearing similar to race in Table 4.

At the time of entry, biopsy material from patients in the surgical group (RP) will be evaluated by the central histology lab. The evaluation will be performed and the results will be recorded on Form 8. Histologic grading will determine the degree of differentiation that can be determined for the tumor. This histologic grade will be summarized as in Table 5. In addition, patients undergoing radical prostatectomy will have descriptive information (including complications) about the procedures recorded (Form 3) as well as pathologic staging by the TNM system. This information is generally recorded as categorical responses and will be summarized as in Table 6 where type of procedure appears as an example.

All patients will be asked to fill out a health status questionnaire at entry and annually thereafter. This questionnaire incorporates the SF-36 Health Status Survey and augments it with the AUA Symptom Index, a Bothersome Index, prostate specific questions (uro-sexual functioning), and items of overall health. These measures consist primarily of rating scales as responses. Individual items will be summarized both by frequency and percent as well as mean rating scores and treatment groups compared by analysis of variance. An example, bodily pain, appears as in Table 7. Composite scores for similar items will be presented with means and standard deviations (as in Table 7) and compared by analysis of variance.

The baseline summaries as described above will permit the monitoring of treatment groups with respect to possible imbalances that may occur in important prognostic variables. Variables so identified will be possible candidates for statistical adjustment procedures at the time of final analysis. The randomization process, in general, works adequately with respect to baseline distributions; nonetheless, the monitoring as outlined in this section will provide an ongoing confirmation of treatment group balance.

### C. Data Quality Reports

The Executive Committee and Study Group will also receive information on selected measures of data quality. This will consist primarily of measures of missing data. In order that the study reach a successful conclusion, the amount of missing data must be minimized with continual efforts directed at reducing rates of missing data to zero. The number of missing forms will be presented as in Table 8 where regularly scheduled forms are listed by form. The percent of missing forms will be based on the expected number due at a given date. These data will provide a general assessment of whether or not centers are following patients adequately as defined by the study protocol and whether corrective action may be indicated. A second type of missing data information that will be presented is missing items per form. These will be given as in Table 9, where the number of missing items per form is presented. As part of the computer editing system, participating centers will receive periodic reports indicating missing values and/or values outside acceptable limits which will then have to be provided or corrected as necessary. An ongoing review by the Executive Committee will serve the purpose of identifying early on any problem areas with the forms or participating centers with respect to data quality.

### III. **MONITORING REPORT TO THE DATA MONITORING BOARD**

The function of the Data Monitoring Board is to serve as the outside or independent review committee that oversees all aspects of the study while ongoing. It includes individuals with demonstrated expertise in the research questions addressed by the study, but who have no role in planning or conducting the study. This committee is empowered to terminate the study if sufficient evidence accumulates to question the general feasibility of continuing. The interim report to this committee will include all the information provided to the Executive Committee as described earlier. In addition, the committee will receive data summaries of accumulating outcome data at regular intervals. The analyses that will be included will be described in the next section on final analysis and will constitute reports of preliminary results.

#### **IV. FINAL ANALYSIS**

##### **A. Study Patient Characteristics at Enrollment**

This section of the report to the Data Monitoring Board will provide descriptive summaries of study patient characteristics at entry into the study. Included will be background and medical history with laboratory results, histologic grading, health status/quality of life. These measures have been reviewed in detail in the previous section of this appendix which discussed the Study Group and Executive Committee Report. The Data Monitoring Board will receive the same material in an ongoing way as it accumulates. The final analysis of these data will include all the analyses as described earlier but on the final and complete data set.

##### **B. Study Follow-up**

Patients enrolled in the study will be followed from the time of randomization until death or completion of the 15-year study period. Routine follow-up visits are scheduled at 6 weeks (one month postop for the RP group), 3, 6, 9, 12 months, and every 6 months thereafter. Data collection during the extensive follow-up period by design will be limited to that which is essential for monitoring the course of prostate cancer. It will include: urologic symptoms and pain assessment, performance status (activities of daily living), annual bone scan, clinical status, tumor staging and size (by DRE) (Form 4); complete documentation of each course of treatment provided for CAP (Form 5); quality of life/health status with urologic symptoms and sexual function (Form 06); and, routine blood monitoring for PSA. The clinical status items listed above (Form 04) are recorded as categorical data and will be summarized and presented as in Table 10 where bone pain appears as an example. Treatment group comparison will be by chi-square procedures. Data summaries will include frequencies by rating period along with change from previous rating periods. The format of Table 10 will also be adopted in presenting PSA which will be classified according to threshold values both for frequencies at each rating period and to characterize change between rating periods. Each time a patient undergoes treatment for CAP, the details will be appropriately recorded (Form 05). These will include the reasons (local, regional, metastatic disease), type (mechanical, surgical, radiation, brachy, or systemic), and response to treatment. This information is recorded as categorical data and summaries will be presented as in Table 11 where

pelvic pain and chemotherapy appear as examples of reason and type of treatment. Comparisons will be by chi-square tests. Patients will be administered the health status questionnaire (Form 6) annually in order to assess quality of life and self perceptions of degree of disability. As noted in an earlier section, the health status questionnaire assesses general and prostate specific aspects of health and daily functioning by employing series of questions for which the responses typically are standard rating scales. Data summaries will be based on composite scores for the different components of the questionnaire that are formed by totaling the appropriate response items. For example, urologic symptoms will be assessed by the AUA (American Urologic Association) Symptom Index comprised of seven questions, each with a six-point rating (0=Not at all, 5=Almost Always) as a response. A total score will be derived and presented as in Table 12. A two-way repeated measures analysis of covariance will be performed in order to compare treatment groups and to evaluate the scores for their response profiles over time.

### C. Mortality

The primary outcome measure for this study is all-cause mortality. The primary statistical analysis will compare the two treatment approaches, radical prostatectomy and expectant management, on the basis of time until death as measured from the date of randomization. Survival curves will be estimated with Kaplan-Meier methodology and will be compared by the logrank statistic.

In addition to all-cause mortality, a secondary objective will be to compare the two management approaches on the basis of prostate cancer specific mortality. Each death will be documented as extensively as possible including autopsy reports, patient chart and narrative summary provided by the PI. Documentation (blinded to treatment group) will be submitted to the Endpoint Committee for final classification as to whether or not the death was prostate cancer related. The same procedure used to evaluate all-cause mortality will then be applied to prostate cancer specific mortality.

In summary, this study has been planned to evaluate two treatment management approaches for localized prostate cancer. Ongoing analyses for the purpose of monitoring as well as final analysis have been described in this Appendix BRDP. This study will be viewed by the medical community as the major definite clinical trial that will determine whether or not radical prostatectomy will be used in the future in treating localized cancer of the prostate.

**TABLE 1**  
**MONTHLY SCREENING RECORD**

MONTH	NUMBER OF PATIENTS			CUMULATIVE NUMBER				
	SCREENED	REJECTED	ENR	SCREENED	REJECTED	ENR	% ENR/EXP	% REJECTED
1								
2								
3								
.								
.								
.								
36								

FIGURE 2

NUMBER OF PATIENTS ENROLLED IN TREATMENT STUDY  
AS PERCENT OF EXPECTED: CUMULATIVE MONTHLY RATES

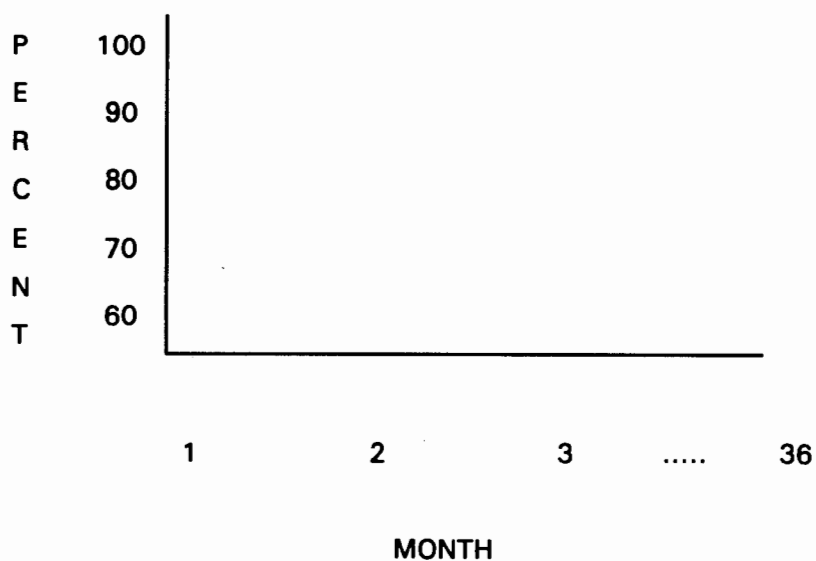


TABLE 2  
CUMULATIVE SCREENING SUMMARY: ALL PATIENTS, BY CENTER

STUDY CENTER	TOTAL NUMBER OF PATIENTS				
	<u>SCREENED</u>	<u>REJECTED</u>	<u>ENROLLED</u>	<u>% OF EXPECTED</u>	<u>% REJECTED</u>
1					
2					
3					
.					
.					
.					
TOTAL					

**TABLE 3**  
**SUMMARY OF INELIGIBILITY: REASONS FOR EXCLUSION,**  
**ALL CENTERS**

REASON	SCREENED	REJECTED:	% of SCR	# Rejected as Only Reason	% of SCR
AGE					
PSA > 100					
BONE SCAN					
NONLOCALIZED CAP					
.					
.					
.					
REFUSAL TOTAL					

**TABLE 4**  
**BACKGROUND HISTORY AT ENTRY**

	RP	EM	P VAL
MEAN AGE (SD)			
RACE			
AMERICAN INDIAN			
ASIAN/PACIFIC ISLANDER			
BLACK/NOT HISPANIC			
WHITE/NOT HISPANIC			
OTHER			
TOTAL			



TABLE 5

CENTRAL HISTOLOGIC EVALUATION AT ENTRY:  
RADICAL PROSTATECTOMY PATIENTS

	#	%
NUMBER OF PATIENTS		
HISTOLOGIC GRADE		
WELL DIFFERENTIATED		
MODERATELY DIFFERENTIATED		
POORLY DIFFERENTIATED/UNDIFFERENTIATED		
UNKNOWN		
TOTAL		

TABLE 6

SUMMARY OF RADICAL PROSTATECTOMY PROCEDURE

	#	%
NUMBER OF PATIENTS		
TYPE OF PROCEDURE		
NERVE SPARING - UNILATERAL		
NERVE SPARING - BILATERAL		
NONNERVE SPARING		

TABLE 7

HEALTH STATUS QUESTIONNAIRE

INDIVIDUAL ITEM	RP		EM		P VAL
	#	%	#	%	
BODILY PAIN/LAST 4 WEEKS					
NONE					
VERY MILD					
MILD					
MODERATE					
SEVERE					
VERY SEVERE					
TOTAL					
MEAN					
S.D.					

TABLE 8

NUMBER AND PERCENT OF MISSING FORMS: BY CENTER

	<u>CENTER 1</u>		<u>CENTER 2</u>		...	<u>CENTER N</u>		<u>TOTAL</u>	
	#	%	#	%		#	%	#	%
FORM									
INFORMED CONSENT									
FORM 1									
Screening									
FORM 2									
Background Information									
.									
.									
.									

TABLE 9

NUMBER AND PERCENT OF FORMS WITH MISSING ITEMS: BY CENTER AND FORM

	<u>CENTER 1</u>		<u>CENTER 2</u>		...	<u>CENTER N</u>		<u>TOTAL</u>	
	#	%	#	%		#	%	#	%
FORM 1									
SCREENING									
.									
.									
.									

TABLE 10  
 CLINICAL STATUS DURING FOLLOW-UP: BONE PAIN

BONE PAIN	SINCE LAST VISIT									
	NEW PAIN					PAIN GONE				
	RP		EM		P-VALUE	RP		EM		
#	%	#	%	#		%	#	%		
MONTH	N	%	N	%	N	%	N	%	N	%
6 (WEEK)										
3										
6										
9										
12										
18										
.										
.										
.										

TABLE 11  
TREATMENT FOR CANCER OF PROSTATE

REASON	RP			EM		P-VALUE
	# PATS	%	# EPISODES	# PATS	%	
PELVIC PAIN						
TYPE						
CHEMOTHERAPY:						
RESPONSE						
CR						
PR						
PROG DZ						
UNK						

TABLE 12

HEALTH STATUS QUESTIONNAIRE

	RP			EM		
	N	MEAN	S.D.	N	MEAN	S.D.
AUA SYMPTOM INDEX						
MONTH PRE						
6 WEEK						
3						
6						
9						
12						
.						
.						
.						

## *Appendix F*

### **CSP #407 Study Forms**

DATA MAILING CHECKLIST

SCREENING REGISTRY

MONTHLY PIVOT SCREENING REGISTRY PAYMENT FORM

FORM 01        SCREENING

FORM 02        BASELINE INFORMATION

FORM 03        SURGICAL

FORM 04        CLINIC VISIT FOLLOW-UP

FORM 05        SUMMARY OF TREATMENT FOR CAP

FORM 06        HEALTH STATUS QUESTIONNAIRE

FORM 07        DEATH OR STUDY TERMINATION

FORM 08        CENTRAL HISTOPATHOLOGIC

FORM 09        BREACH OF PROTOCOL







VA/NCI COOPERATIVE STUDY NO. 407 - PIVOT

PIVOT SCREENING REGISTRY

Medical Center Name \_\_\_\_\_ VA Medical Center No. \_\_\_\_\_  
 NCI Institute No./Affiliate No. \_\_\_\_\_ / \_\_\_\_\_  
 NCI Group (1=CALGB, 2=ECOG, 3=SWOG) \_\_\_\_\_

**INSTRUCTIONS:** All patients with a diagnosis of prostate cancer should be included on this log. Patients not excluded<sup>1</sup> at registry review should be screened for entry in the study. Mail to the Coordinating Center when all lines on a page are completed.

Screen No.	Name (Last, First)	Social Security No.	Date of Birth (Mo/Day/Yr)	Race <sup>2</sup>	Date of Biopsy (Mo/Yr)	Histo-logic Grade <sup>3</sup>	PSA (ng/ml)	Clinically Localized? 1=Yes 2=No	Randomized? 1=Yes 2=No	Initial Therapy <sup>4</sup>
9001	_____	_____	_____	_____	_____	_____	_____	_____	_____	_____
9002	_____	_____	_____	_____	_____	_____	_____	_____	_____	_____
9003	_____	_____	_____	_____	_____	_____	_____	_____	_____	_____
9004	_____	_____	_____	_____	_____	_____	_____	_____	_____	_____
9005	_____	_____	_____	_____	_____	_____	_____	_____	_____	_____
9006	_____	_____	_____	_____	_____	_____	_____	_____	_____	_____
9007	_____	_____	_____	_____	_____	_____	_____	_____	_____	_____
9008	_____	_____	_____	_____	_____	_____	_____	_____	_____	_____
9009	_____	_____	_____	_____	_____	_____	_____	_____	_____	_____
9010	_____	_____	_____	_____	_____	_____	_____	_____	_____	_____
9011	_____	_____	_____	_____	_____	_____	_____	_____	_____	_____
9012	_____	_____	_____	_____	_____	_____	_____	_____	_____	_____
9013	_____	_____	_____	_____	_____	_____	_____	_____	_____	_____
9014	_____	_____	_____	_____	_____	_____	_____	_____	_____	_____

<sup>1</sup> Exclusion Criteria: Age > 75; nonlocalized CAP; Dx of CAP > 6 months; PSA > 50; positive bone scan; life expectancy < 10 years; CAP Rx other than TURP/TUIP/simple prost.

<sup>2</sup> Race

- 1 = American Indian or Alaskan Native
- 2 = Asian or Pacific Islander
- 3 = Black, not of Hispanic origin
- 4 = Hispanic
- 5 = White, not of Hispanic origin
- 6 = Other, specify \_\_\_\_\_

<sup>3</sup> Histologic Grade:

- 1 = Well differentiated
- 2 = Moderately well differentiated
- 3 = Poorly differentiated/Undifferentiated
- 9 = Unknown

<sup>4</sup>Initial Therapy

- 1 = Radical prostatectomy
- 2 = Expectant management
- 3 = Radiation
- 4 = Hormone
- 5 = Cryotherapy
- 6 = Brachytherapy
- 7 = Chemotherapy
- 8 = Other

**VA/NCI COOPERATIVE STUDY NO. 407 - PIVOT**

**MONTHLY PIVOT SCREENING REGISTRY PAYMENT FORM**

Medical Center Name \_\_\_\_\_ VA Medical Center No. \_\_\_\_\_

NCI Institute No./Affiliate No. \_\_\_\_\_ / \_\_\_\_\_

NCI Group (1=CALGB, 2=ECOG, 3=SWOG) \_\_\_\_\_

Date Completed \_\_\_\_ / \_\_\_\_ / \_\_\_\_

**INSTRUCTIONS: PAYMENT FOR MONTHLY SCREENING REGISTRIES WILL BE BASED ON TIMELY SUBMISSION OF THIS FORM.**

*[The individual patient screening information is to be submitted directly on the Pivot Screening Registry when all "Screen No." (9000 Series) lines have been completed.]*

1. Month and year of this Screening Registry Summary . . . . . MO \_\_\_\_ YR \_\_\_\_
  
2. Number of patients with prostate cancer entered on the Pivot Screening Registry for this month . . . . . \_\_\_\_\_
  - a. Enter the "Screening No." (9000 series from Pivot Registry) of the **FIRST** . . . . . \_\_\_\_\_
  - b. Enter the "Screening No." of the **LAST** . . . . . \_\_\_\_\_

Medical Center Name \_\_\_\_\_

VA Medical Center No. \_\_\_\_\_

NCI Institute No./Affiliate No. \_\_\_\_\_ / \_\_\_\_\_

NCI Group (1=CALGB, 2=ECOG, 3=SWOG) \_\_\_\_\_

Patient Name \_\_\_\_\_

Screening No. \_\_\_\_\_

S.S.# \_\_\_\_\_ - \_\_\_\_\_ - \_\_\_\_\_

Patient No. \_\_\_\_\_

Date Completed Mo \_\_\_\_ Day \_\_\_\_ Yr \_\_\_\_

**INSTRUCTIONS: THIS FORM SHOULD BE COMPLETED ON ALL PATIENTS WITH A DIAGNOSIS OF PROSTATE CANCER WHO WERE SCREENED FOR ENTRY INTO THIS STUDY.**

1= YES  
2= NO  
3= NS\*

**A. EXCLUSION CRITERIA**

(\*NS=Not Screened)

- 1. Age more than 75 years . . . . . \_\_\_\_\_
- 2. PSA > 50 ng/ml (or, if on 5-alpha reductase inhibitor, PSA > 25 ng/ml) . . . . . \_\_\_\_\_
- 3. Bone scan consistent with metastatic disease . . . . . \_\_\_\_\_
- 4. Other imaging or laboratory studies indicating that prostate cancer is nonlocalized . . . . . \_\_\_\_\_
- 5. Other evidence that cancer of the prostate is not clinically localized . . . . . \_\_\_\_\_
- 6. Diagnosis of prostate cancer greater than 6 months ago . . . . . \_\_\_\_\_
- 7. Significant coexisting medical conditions or high surgical risks:
  - A. Life expectancy less than 10 years . . . . . \_\_\_\_\_
  - B. Serum creatinine greater than 3 mg/dl . . . . . \_\_\_\_\_
  - C. Myocardial infarction within last 6 months . . . . . \_\_\_\_\_
  - D. Unstable angina . . . . . \_\_\_\_\_
  - E. New York Heart Association Class III or IV congestive heart failure . . . . . \_\_\_\_\_
  - F. Severe pulmonary disease . . . . . \_\_\_\_\_
  - G. Liver failure . . . . . \_\_\_\_\_
  - H. Severe dementia . . . . . \_\_\_\_\_
  - I. Debilitating illness . . . . . \_\_\_\_\_
  - J. Malignancies, except for nonmelanomatous skin cancer nonrecurring in the last 5 years . . . . . \_\_\_\_\_
- 8. Prior therapy for CAP (pelvic irradiation, chemotherapy, anti-androgen or androgen deprivation therapy except 5-alpha reductase inhibitors [Proscar]) . . . . . \_\_\_\_\_
- 9. Prostate surgery other than TURP/TUIP/simple prostatectomy . . . . . \_\_\_\_\_
- 10. Current use of estrogens or androgen blocking drugs . . . . . \_\_\_\_\_
- 11. Uncooperative or unreliable patient . . . . . \_\_\_\_\_
- 12. Participating in another interventional study . . . . . \_\_\_\_\_

**B. INFORMED CONSENT**

- 13. Did patient view the informational video? (1=Yes, 2=No) . . . . . \_\_\_\_\_
- 14. Did patient sign consent form for participation in the study? (1=Yes, 2=No) . . . . . \_\_\_\_\_

IF PATIENT SIGNED THE INFORMED CONSENT, GO TO SECTION C.

If the patient refuses to sign informed consent, which of the following reasons was the major reason for refusal and which were contributing, but not major problems.

**1=Not a factor**  
**2=Major factor**  
**3=Contributing, but not major**

- 15. Patient not willing to participate in research of any kind . . . . . \_\_\_\_\_
- 16. Patient not willing to receive "experimental" form of therapy . . . . . \_\_\_\_\_
- 17. Patient fears participating will interfere with receiving proper treatment . . . . . \_\_\_\_\_
- 18. Patient not willing to leave decision for treatment to chance . . . . . \_\_\_\_\_
- 19. Patient prefers treatment elsewhere . . . . . \_\_\_\_\_
- 20. Patient declines for other reason \_\_\_\_\_  
Specify \_\_\_\_\_
- 21. Physician prefers that patient not participate . . . . . \_\_\_\_\_
- 22. Others (family, etc.) prefer that patient not participate . . . . . \_\_\_\_\_

**C. RANDOMIZATION STATUS**

- 23. Patient's randomization status . . . . . \_\_\_\_\_  
(1=Ineligible, 2=Eligible, Declines Randomization, 3=Randomized into study)

IF IN STUDY:

- 24. Date randomized . . . . . Mo\_\_ Day\_\_ Yr\_\_
- 25. Patient's randomization number (Patient No.) . . . . . \_\_\_\_\_

**PLEASE ENTER PATIENT NO. ON TOP OF BOTH PAGES OF THIS FORM.**

P.I.'s Signature \_\_\_\_\_

**VA/NCI COOPERATIVE STUDY #407 - PIVOT BASELINE INFORMATION FORM 02**

(Page 1 of 3)

Medical Center Name \_\_\_\_\_ VA Medical Center No. \_\_\_\_\_  
 NCI Institute No./Affiliate No. \_\_\_\_\_ / \_\_\_\_\_  
 NCI Group (1=CALGB, 2=ECOG, 3=SWOG) \_\_\_\_\_  
 Patient Name \_\_\_\_\_ Patient No. \_\_\_\_\_  
 Date Completed: Mo \_\_\_\_\_ Day \_\_\_\_\_ Yr \_\_\_\_\_

**A. PATIENT PROFILE**

1. Date of birth . . . . . Mo \_\_\_\_\_ Day \_\_\_\_\_ Yr \_\_\_\_\_
2. Race . . . . . \_\_\_\_\_  
 1 = American Indian or Alaskan Native  
 2 = Asian or Pacific Islander  
 3 = Black, not of Hispanic origin  
 4 = Hispanic  
 5 = White, not of Hispanic origin  
 6 = Other, specify \_\_\_\_\_
3. Family history of CAP? (1 = Yes, 2 = No) . . . . . \_\_\_\_\_
4. What led to the prostate tissue sampling? . . . . . \_\_\_\_\_  
 1 = Bladder outlet obstructive symptoms                      4 = Abnormal TRUS  
 2 = Other symptoms    5 = Elevated PSA  
 3 = Abnormal digital rectal exam                                      6 = Change in PSA

**B. MARITAL STATUS** . . . . . \_\_\_\_\_

- |               |                   |
|---------------|-------------------|
| 1 = Married   | 4 = Separated     |
| 2 = Remarried | 5 = Divorced      |
| 3 = Widowed   | 6 = Never married |

**C. HIGHEST LEVEL OF EDUCATION ATTAINED** . . . . . \_\_\_\_\_

- |   |  |
|---|--|
| 1 = Under 7 years of schooling            | 5 = Partial college training                 |
| 2 = Junior high school (7th-9th grade)    | 6 = Standard college/university graduate     |
| 3 = Partial high school (10th-11th grade) | 7 = Completed graduate/professional training |
| 4 = High school graduate                  |  |

**D. PERFORMANCE STATUS**

5. Please describe the patient's activities of daily living . . . . . \_\_\_\_\_  
 0 = Fully active  
 1 = Symptoms but ambulatory and able to do light work  
 2 = No work but self care and active 50% of waking hours  
 3 = Limited self care, confined to bed or chair > 50% of waking hours  
 4 = Completely disabled

**E. SMOKING HISTORY**

6. Pack years (packs per day X years smoking) of smoking cigarettes . . . . . \_\_\_\_\_  
 (Nonsmokers code = 000)  
 A. Does patient smoke cigarettes now? (1 = Yes, 2 = No) . . . . . \_\_\_\_\_

1= YES

2= NO

F. CHARLSON SCORE

- 7. Has patient ever had a myocardial infarction? \_\_\_\_\_
- 8. History of chronic congestive heart failure? \_\_\_\_\_
- 9. History or current evidence of peripheral vascular disease? \_\_\_\_\_
- 10. History or current evidence of cerebrovascular disease? \_\_\_\_\_
- 11. Has patient ever had a stroke? \_\_\_\_\_
- 12. History of diabetes? \_\_\_\_\_
  - A. If Yes, end organ damage? \_\_\_\_\_
- 13. History or current evidence of dementia? \_\_\_\_\_
- 14. History or current evidence of chronic pulmonary disease? \_\_\_\_\_
- 15. History or current evidence of connective tissue disease? \_\_\_\_\_
- 16. History or current evidence of peptic ulcer disease? \_\_\_\_\_
- 17. History or current evidence of mild liver disease? \_\_\_\_\_
- 18. History or current evidence of moderate or severe liver disease? \_\_\_\_\_
- 19. History or current evidence of moderate or severe renal disease? \_\_\_\_\_
- 20. History of cancer (other than skin, prostate, or non-invasive bladder cancer)? \_\_\_\_\_
  - A. If Yes, type of tumor (1=Leukemia, 2=Lymphoma, 3=Metastatic solid tumor, 4=Any other) . . . \_\_\_\_\_
- 21. History or current evidence of AIDS or ARC? \_\_\_\_\_

G. OTHER MEDICAL HISTORY

1= YES

2= NO

- 22. Has patient had treatment for BPH? \_\_\_\_\_
  - IF YES, indicate treatments:
  - A. Watchful waiting \_\_\_\_\_
  - B. Alpha blocker \_\_\_\_\_
  - C. 5-alpha-reductase \_\_\_\_\_
  - D. TURP/TUIP \_\_\_\_\_
  - E. Open simple prostatectomy \_\_\_\_\_
  - F. Other surgical, specify \_\_\_\_\_
- 23. Has the patient had a vasectomy? \_\_\_\_\_



Medical Center Name \_\_\_\_\_

VA Medical Center No. \_\_\_\_\_

NCI Institute No./Affiliate No. \_\_\_\_\_ / \_\_\_\_\_

NCI Group (1=CALGB, 2=ECOG, 3=SWOG) \_\_\_\_\_

Patient Name \_\_\_\_\_

Patient No. \_\_\_\_\_

Date Completed: Mo \_\_\_ Day \_\_\_ Yr \_\_\_

**INSTRUCTIONS: COMPLETE THIS FORM AND SUBMIT WITHIN 30 DAYS OF SURGERY. RECORD ANY SURGICAL COMPLICATIONS THAT OCCUR WITHIN 30 DAYS OF SURGERY OR PRIOR TO DISCHARGE ON PAGE 3 OF THIS FORM.**

**A. BIOPSY OR FINE NEEDLE ASPIRATION (FNA)**

1. Date of original diagnostic biopsy/FNA . . . . . Mo \_\_\_ Day \_\_\_ Yr \_\_\_

**NOTE: Biopsy should be sent to Central Pathology Laboratory.**

**B. PELVIC LYMPH NODE DISSECTION**

2. Was the pelvic lymph node dissection done? (1=Yes, 2=No, 3=Unknown) . . . . . \_\_\_\_\_

A. If NO, why not? \_\_\_\_\_

If YES, complete the following:

B. Date of pelvic lymph node dissection . . . . . Mo \_\_\_ Day \_\_\_ Yr \_\_\_

C. Pathologic nodal status (1=Negative, 2=Positive, 3=Unknown) . . . . . \_\_\_\_\_

D. Were the nodes resectable? (1=Yes, 2=No, 3=Unknown) . . . . . \_\_\_\_\_

E. Were the external iliac nodes dissected? (1=Yes, 2=No, 3=Unknown) . . . . . \_\_\_\_\_

F. Were the hypogastric obturator nodes dissected? (1=Yes, 2=No, 3=Unknown) . . . . . \_\_\_\_\_

**C. PROSTATECTOMY**

3. Was the prostatectomy done? (1=Yes, 2=No, 3=Unknown) . . . . . \_\_\_\_\_

If NO, complete the following:

A. Indicate reason . . . . . \_\_\_\_\_

- 1=Patient refusal
- 2=MD recommendation
- 3=New diagnosis of high surgical risk
- 4=Alternative therapy for prostate cancer
- 5=CAP extending outside of prostate gland
- 6=Other, specify \_\_\_\_\_

B. Describe reason for no surgery (cancellation): \_\_\_\_\_

If YES, complete the following:

C. Date of prostatectomy . . . . . Mo \_\_\_ Day \_\_\_ Yr \_\_\_

D. Type of surgical approach (1=Retropubic, 2=Perineal) . . . . . \_\_\_\_\_



E. Type of procedure ..... \_\_\_\_\_

- 1 = Nerve-sparing unilateral
- 2 = Nerve-sparing bilateral
- 3 = Non-nerve-sparing

F. Was the prostate removed? (1=Yes, 2=No, 3=Unknown) ..... \_\_\_\_\_

G. Were the seminal vesicles and ampulla of the vas removed? (1=Yes, 2=No, 3=Unknown) . . . \_\_\_\_\_

H. Was prostatectomy done on an Expectant Management patient? (1=Yes, 2=No) . . . . . \_\_\_\_\_

If yes, complete Breach of Protocol, Form 09

4. Was prostatectomy delayed/cancelled? (1=Yes, 2=No, 3=Unknown) ..... \_\_\_\_\_

A. If YES, indicate reason ..... \_\_\_\_\_

- 1 = Patient/personal reasons
- 2 = MD recommendation
- 3 = Intercurrent clinical event
- 4 = Study related
- 5 = Downstaging with hormone therapy
- 6 = Other, specify \_\_\_\_\_

B. Describe reason for delay: \_\_\_\_\_  
 \_\_\_\_\_

5. Pathologic stage of disease ..... T = \_\_\_\_\_ N = \_\_\_\_\_ M = \_\_\_\_\_

<u>T</u>	<u>N</u>	<u>M</u>
X	X	X
0	0	0
1a (A1)	1 (D1)	1a (D2)
1b (A2)	2 (D1)	1b (D2)
1c	3	1c (D2)
2a (B1)		
2b (B2)		
2c (B3)		
3a (C1)		
3b (C1)		
3c (C1)		
4a (C2)		
4b (C2)		

6. Pathologic extent of disease ..... \_\_\_\_\_

- 1 = Confined to prostate
- 2 = Capsular invasion
- 3 = Capsular penetration
- 4 = Surgical margins involved
- 5 = Seminal vesicle invasion
- 6 = Metastatic disease
- 7 = Unknown

A. If "6" above, was metastatic site biopsy proven? (1=Yes, 2=No) ..... \_\_\_\_\_

**D. SURGICAL COMPLICATIONS**

7. Did any surgical complications occur within 30 days of surgery? (1=Yes, 2=No) . . . . . \_\_\_\_\_

If YES, complete the following:

1=Yes  
2=No

1=Yes  
2=No

*Infections requiring antibiotics:*

- A. Pneumonia \_\_\_\_\_
- B. Wound infection \_\_\_\_\_
- C. Urinary tract infection \_\_\_\_\_
- D. Sepsis \_\_\_\_\_
- E. Bacteremia \_\_\_\_\_
- F. Deep vein thrombosis \_\_\_\_\_
- G. Stroke \_\_\_\_\_
- H. Pulmonary embolus \_\_\_\_\_
- I. Renal failure requiring dialysis \_\_\_\_\_

- J. Postoperative bleeding requiring transfusion \_\_\_\_\_
- K. MI by enzymes or ECG \_\_\_\_\_
- L. Bowel injury requiring surgical repair \_\_\_\_\_
- M. Catheter device present > 30 days post-op \_\_\_\_\_
- N. Death \_\_\_\_\_
- O. Additional surgical repair,  
specify \_\_\_\_\_
- P. Other, \_\_\_\_\_  
specify \_\_\_\_\_

P.I.'s Signature \_\_\_\_\_

**VA/NCI COOPERATIVE STUDY #407 - PIVOT CLINIC VISIT FOLLOW-UP FORM 04**

(Page 1 of 2)

Medical Center Name \_\_\_\_\_ VA Medical Center No. \_\_\_\_\_  
 NCI Institute No./Affiliate No. \_\_\_\_\_/\_\_\_\_\_  
 NCI Group (1=CALGB, 2=ECOG, 3=SWOG) \_\_\_\_\_  
 Patient Name \_\_\_\_\_ Patient No. \_\_\_\_\_  
 Date Completed: Mo \_\_\_\_\_ Day \_\_\_\_\_ Yr \_\_\_\_\_

ENTER APPROPRIATE VISIT NUMBER FROM CODES ON LAST PAGE (BOND SHEET) . . . . . \_\_\_\_\_

1. Did patient come in for clinic visit? (1=Yes, 2=No) . . . . . \_\_\_\_\_

If YES:

A. Date of visit . . . . . Mo \_\_\_\_\_ Day \_\_\_\_\_ Yr \_\_\_\_\_

2. Since last visit, has patient had any of the following:

- A. Blood in urine . . . . . \_\_\_\_\_
- B. Difficulty with starting or with force of urination . . . . . \_\_\_\_\_
- C. Incomplete control of urine . . . . . \_\_\_\_\_
- D. Swelling in legs . . . . . \_\_\_\_\_
- E. Change in bowel movements . . . . . \_\_\_\_\_
- F. Bone pain . . . . . \_\_\_\_\_
- G. Pelvic pain . . . . . \_\_\_\_\_
- H. Weight loss . . . . . \_\_\_\_\_
- I. Weakness . . . . . \_\_\_\_\_
- J. Fatigue . . . . . \_\_\_\_\_
- K. Impotence . . . . . \_\_\_\_\_
- L. Nausea . . . . . \_\_\_\_\_
- M. Other (describe) \_\_\_\_\_

1= YES  
2= NO

**IF YES:**  
**CAP related?**  
1= YES  
2= NO

**PERFORMANCE STATUS**

3. Please describe the patient's activities of daily living since last visit . . . . . \_\_\_\_\_

- 0=Fully active
- 1=Symptoms but ambulatory and able to do light work
- 2=No work but self care and active 50% of waking hours
- 3=Limited self care, confined to bed or chair > 50% of waking hours
- 4=Completely disabled

**BONE SCAN - TO BE DONE ANNUALLY.**

4. Bone scan ..... \_\_\_\_\_  
 1 = Normal  
 2 = Abnormal, not suggestive of malignancy  
 3 = Abnormal, suggestive of malignancy  
 4 = Definitely malignant (axial skeleton only)  
 5 = Definitely malignant (> 1 site)
5. Date of bone scan ..... Mo \_\_\_\_\_ Day \_\_\_\_\_ Yr \_\_\_\_\_

**FOLLOW-UP TREATMENT/HOSPITALIZATION FOR CAP**

6. Did patient receive treatment for CAP since last visit? (1 = Yes, 2 = No) ..... \_\_\_\_\_  
 (If Yes, complete Form 05, Summary of Treatment for CAP.)
7. Compared to last visit, how would you describe the patient's clinical status with regard to CAP? ..... \_\_\_\_\_  
 1 = Clinically stable, no evidence of disease  
 2 = Clinically stable, disease present  
 3 = Disease has recurred/progressed but asymptomatic  
 4 = Recurred/progressed and causing clinical signs/symptoms  
 A. If "2", "3" or "4" above, is disease currently: (1 = Local, 2 = Regional, 3 = Systemic) ..... \_\_\_\_\_
8. Was patient hospitalized since last visit? (1 = Yes, 2 = No) ..... \_\_\_\_\_  
 A. If Yes, was hospitalization related to CAP or CAP therapy? (1 = Yes, 2 = No) ..... \_\_\_\_\_  
 (If Yes, complete Form 05, Summary of Treatment for CAP.)

**CLINICAL STAGING INFORMATION**

9. Clinical stage of disease ..... T = \_\_\_\_\_ N = \_\_\_\_\_ M = \_\_\_\_\_

<u>T</u>	<u>N</u>	<u>M</u>
X	X	X
0	0	0
1a (A1)	1 (D1)	1a (D2)
1b (A2)	2 (D1)	1b (D2)
1c	3	1c (D2)
2a (B1)		
2b (B2)		
2c (B3)		
3a (C1)		
3b (C1)		
3c (C1)		
4a (C2)		
4b (C2)		

10. Tumor size (digital rectal exam) ..... \_\_\_\_\_  
 1 = Not palpable  
 2 = Palpable but tumor ≤ 1.5 cm in greatest dimension  
 3 = > 1.5 cm in greatest dimension  
 4 = Not stated/unknown

P.I.'s Signature \_\_\_\_\_

**CODES FOR VISIT NUMBERS**

*CSP #407*

*Prostate Cancer Intervention Versus Observation Trial (PIVOT)*

00 = RANDOMIZATION VISIT  
01 = 6 WEEKS  
02 = 3 MONTHS  
03 = 6 MONTHS  
04 = 9 MONTHS  
05 = 12 MONTHS  
06 = YEAR 2 - VISIT 1 (18 months)  
07 = YEAR 2 - VISIT 2 (24 months)  
08 = YEAR 3 - VISIT 1 (30 months)  
09 = YEAR 3 - VISIT 2 (36 months)  
10 = YEAR 4 - VISIT 1  
11 = YEAR 4 - VISIT 2  
12 = YEAR 5 - VISIT 1  
13 = YEAR 5 - VISIT 2  
14 = YEAR 6 - VISIT 1  
15 = YEAR 6 - VISIT 2  
16 = YEAR 7 - VISIT 1  
17 = YEAR 7 - VISIT 2  
18 = YEAR 8 - VISIT 1  
19 = YEAR 8 - VISIT 2  
20 = YEAR 9 - VISIT 1  
21 = YEAR 9 - VISIT 2  
22 = YEAR 10 - VISIT 1  
23 = YEAR 10 - VISIT 2  
24 = YEAR 11 - VISIT 1  
25 = YEAR 11 - VISIT 2  
26 = YEAR 12 - VISIT 1  
27 = YEAR 12 - VISIT 2  
28 = YEAR 13 - VISIT 1  
29 = YEAR 13 - VISIT 2  
30 = YEAR 14 - VISIT 1  
31 = YEAR 14 - VISIT 2  
32 = YEAR 15 - VISIT 1  
33 = YEAR 15 - VISIT 2  
99 = UNSCHEDULED VISIT

**VA/NCI COOPERATIVE STUDY #407 - PIVOT**

**SUMMARY OF TREATMENT FOR CAP FORM 05**

(Page 1 of 4)

Medical Center Name \_\_\_\_\_ VA Medical Center No. \_\_\_\_\_

NCI Institute No./Affiliate No. \_\_\_\_\_ / \_\_\_\_\_

NCI Group (1=CALGB, 2=ECOG, 3=SWOG) \_\_\_\_\_

Patient Name \_\_\_\_\_ Patient No. \_\_\_\_\_

Date Completed: Mo \_\_\_\_\_ Day \_\_\_\_\_ Yr \_\_\_\_\_

*INSTRUCTIONS: THIS FORM MUST BE COMPLETED EACH TIME A PATIENT UNDERGOES NEW TREATMENT FOR CAP. PATIENTS IN EXPECTANT MANAGEMENT GROUP SHOULD HAVE TREATMENT ONLY IF DISEASE IS SYMPTOMATIC OR METASTATIC. RADICAL PROSTATECTOMY OR RADIATION THERAPY IN EXPECTANT MANAGEMENT GROUP IS CONSIDERED PROTOCOL VIOLATION UNLESS UTILIZED FOR PALLIATION OF SYMPTOMS.*

**1=YES  
2=NO**

**REASONS FOR TREATMENT FOR PROSTATE CANCER**

Local Disease:

- 1. Persistent tumor despite prostatectomy . . . . . \_\_\_\_\_
- 2. New mass on DRE/TRUS or other imaging study . . . . . \_\_\_\_\_
- 3. Enlarging mass on DRE/TRUS or other imaging study . . . . . \_\_\_\_\_
- 4. Hematuria due to CAP . . . . . \_\_\_\_\_
- 5. Bladder outlet obstruction due to CAP . . . . . \_\_\_\_\_

IF YES:

- A. AUA symptom score 20 . . . . . \_\_\_\_\_
- B. Bothersome score  $\geq$  "a lot" . . . . . \_\_\_\_\_
- C. Creatinine 2X baseline or  $\geq$  3.0 mg/dl . . . . . \_\_\_\_\_

- 6. Other (describe) \_\_\_\_\_ . . . . . \_\_\_\_\_

Regional Disease:

- 7. Persistent tumor despite prostatectomy . . . . . \_\_\_\_\_
- 8. Ureteral obstruction with hydronephrosis . . . . . \_\_\_\_\_
  - A. If Yes, creatinine 2X baseline or  $\geq$  3.0 mg/dl . . . . . \_\_\_\_\_
- 9. Pelvic pain . . . . . \_\_\_\_\_
- 10. Lymph edema . . . . . \_\_\_\_\_
- 11. Rectal obstruction . . . . . \_\_\_\_\_
- 12. Other (describe) \_\_\_\_\_ . . . . . \_\_\_\_\_

Metastatic Disease:

- 13. Positive bone scan . . . . . \_\_\_\_\_
- 14. Positive roentgenograms . . . . . \_\_\_\_\_
- 15. Increase in liver function tests and positive imaging study . . . . . \_\_\_\_\_
- 16. Anemia . . . . . \_\_\_\_\_
- 17. Reduction in functional status . . . . . \_\_\_\_\_
- 18. Other (describe) \_\_\_\_\_ . . . . . \_\_\_\_\_

1=YES

2=NO

Abnormal Biomarkers:

- 19. Increasing or persistent PSA ..... \_\_\_\_\_
- 20. Sexual Dysfunction ..... \_\_\_\_\_
- 21. Incontinence ..... \_\_\_\_\_
- 22. Other, specify \_\_\_\_\_ .....

**TYPE OF FOLLOW-UP INTERVENTION FOR PROSTATE CANCER SINCE LAST VISIT.**

1=YES

2=NO

- 23. MECHANICAL ..... \_\_\_\_\_

A. If Yes, specify types:

- 1. TURP ..... \_\_\_\_\_
- 2. TUIP ..... \_\_\_\_\_
- 3. Stent (type) \_\_\_\_\_ .....
- 4. Other, specify \_\_\_\_\_ .....

1=YES

2=NO

- 24. SURGERY ..... \_\_\_\_\_

A. If Yes, specify procedures:

- 1. Pelvic lymphadenectomy ..... \_\_\_\_\_
- 2. Simple prostatectomy ..... \_\_\_\_\_
- 3. Standard radical prostatectomy ..... \_\_\_\_\_
- 4. Nerve sparing prostatectomy ..... \_\_\_\_\_
- 5. Perineal prostatectomy ..... \_\_\_\_\_
- 6. Other \_\_\_\_\_ .....
- 7. Unknown ..... \_\_\_\_\_

25. RADIATION (1 = Yes, 2 = No) . . . . . \_\_\_\_\_

IF YES:

A. Prostate (1 = Yes, 2 = No) . . . . . \_\_\_\_\_

IF YES:

1. Type (1 = External beam, 2 = Interstitial, 3 = Unknown) . . . . . \_\_\_\_\_

2. Best response (1 = CR, 2 = PR, 3 = Progressive DZ, 4 = Unknown) . . . . . \_\_\_\_\_

B. Pelvic lymph nodes (1 = Yes, 2 = No) . . . . . \_\_\_\_\_

IF YES:

1. Type (1 = External beam, 2 = Interstitial, 3 = Unknown) . . . . . \_\_\_\_\_

2. Best response (1 = CR, 2 = PR, 3 = Progressive DZ, 4 = Unknown) . . . . . \_\_\_\_\_

C. Parenchymal (1 = Yes, 2 = No) . . . . . \_\_\_\_\_

IF YES:

1. Specify location \_\_\_\_\_

2. Type (1 = External beam, 2 = Interstitial, 3 = Unknown) . . . . . \_\_\_\_\_

3. Best response (1 = CR, 2 = PR, 3 = Progressive DZ, 4 = Unknown) . . . . . \_\_\_\_\_

D. Bone (1 = Yes, 2 = No) . . . . . \_\_\_\_\_

IF YES:

1. Specify \_\_\_\_\_

2. Type (1 = External beam, 2 = Interstitial, 3 = Unknown) . . . . . \_\_\_\_\_

3. Best response (1 = CR, 2 = PR, 3 = Progressive DZ, 4 = Unknown) . . . . . \_\_\_\_\_

26. BRACHY THERAPY (1 = Yes, 2 = No) . . . . . \_\_\_\_\_

IF YES: Best response (1 = CR, 2 = PR, 3 = Progressive DZ, 4 = Unknown) . . . . . \_\_\_\_\_

27. CRYOTHERAPY (1 = Yes, 2 = No) . . . . . \_\_\_\_\_

IF YES: Best response (1 = CR, 2 = PR, 3 = Progressive DZ, 4 = Unknown) . . . . . \_\_\_\_\_



28. SYSTEMIC THERAPY SINCE LAST VISIT (1=Yes, 2=No) .....

IF YES:

Best Response

1=CR

2=PR

3=Progressive DZ

4=Unknown

1=Yes

2=No

TYPE OF THERAPY

Other Systemic Therapy:

- A. Alpha Blockers ..... \_\_\_\_\_
- B. Chemotherapy ..... \_\_\_\_\_
- C. Immunotherapy ..... \_\_\_\_\_

Hormone Therapy:

- D. Orchiectomy ..... \_\_\_\_\_
- E. Adrenalectomy ..... \_\_\_\_\_
- F. Hypophysectomy ..... \_\_\_\_\_
- G. DES/estrogen ..... \_\_\_\_\_
- H. LHRH analog ..... \_\_\_\_\_
- I. Antiandrogens ..... \_\_\_\_\_
- J. Other hormone Rx ..... \_\_\_\_\_

Therapy for Sexual Dysfunction:

- K. Penile injection ..... \_\_\_\_\_
- L. Prosthesis ..... \_\_\_\_\_
- M. Vacuum device ..... \_\_\_\_\_
- N. Other \_\_\_\_\_ .....

Therapy for Incontinence:

- O. Teflon or collagen injections ..... \_\_\_\_\_
- P. Artificial sphincters ..... \_\_\_\_\_
- Q. Catheter device ..... \_\_\_\_\_
- R. Pads ..... \_\_\_\_\_
- S. Clamps ..... \_\_\_\_\_
- T. Other \_\_\_\_\_ .....

29. Did any of the above treatment involve unauthorized surgery, radiation, procedures, or other therapies on an expectant management patient? (1=Yes, 2=No) .....

**IF YES, COMPLETE "BREACH OF PROTOCOL FORM 09"**

P.I.'s Signature \_\_\_\_\_

**VA/NCI COOPERATIVE STUDY #407 - PIVOT**

**HEALTH STATUS QUESTIONNAIRE FORM 06**

(Page 1 of 8)

Medical Center Name \_\_\_\_\_ VA Medical Center No. \_\_\_\_\_

NCI Institute No./Affiliate No. \_\_\_\_\_ / \_\_\_\_\_

NCI Group (1=CALGB, 2=ECOG, 3=SWOG) \_\_\_\_\_

Patient Name \_\_\_\_\_ Visit No. \_\_\_\_\_ Patient No. \_\_\_\_\_

Date Completed: Mo \_\_\_\_\_ Day \_\_\_\_\_ Yr \_\_\_\_\_

*Answer every question by marking the appropriate box. If you are unsure about how to answer a question please give the best answer you can.*

**A. SF-36™ HEALTH STATUS SURVEY**

1. In general, would you say your health is:  
(circle one number)

- |   |           |
|---|-----------|
| 1 | Excellent |
| 2 | Very Good |
| 3 | Good      |
| 4 | Fair      |
| 5 | Poor      |

2. Compared to one year ago, how would you rate your health in general now?  
(circle one number)

- |   |                                     |
|---|-------------------------------------|
| 1 | Much better now than 1 year ago     |
| 2 | Somewhat better now than 1 year ago |
| 3 | About the same                      |
| 4 | Somewhat worse now than 1 year ago  |
| 5 | Much worse now than 1 year ago      |

3. 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 one number on each line)

- a. Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports .....
- b. Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf .....
- c. Lifting or carrying groceries .....

	Yes, Limited A Lot	Yes, Limited A Little	No, Not Limited At All
a.	1	2	3
b.	1	2	3
c.	1	2	3

- d. Climbing several flights of stairs . . . . .
- e. Climbing one flight of stairs . . . . .
- f. Bending, kneeling, or stooping . . . . .
- g. Walking more than a mile . . . . .
- h. Walking several blocks . . . . .
- i. Walking one block . . . . .
- j. Bathing or dressing yourself . . . . .

	Yes, Limited A Lot	Yes, Limited A Little	No, Not Limited At All
d.	1	2	3
e.	1	2	3
f.	1	2	3
g.	1	2	3
h.	1	2	3
i.	1	2	3
j.	1	2	3

4. 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 physical health?  
*(circle one number on each line)*

- a. Cut down the amount of time you spent on work or other activities . . . . .
- b. Accomplished less than you would like . . . . .
- c. Were limited in the kind of work or other activities . . . . .
- d. Had difficulty performing the work or other activities (for example, it took extra effort) . . . . .

	YES	NO
a.	1	2
b.	1	2
c.	1	2
d.	1	2

5. 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 any emotional problems such as feeling depressed or anxious? *(circle one number on each line)*

- a. Cut down the amount of time you spent on work or other activities . . . . .
- b. Accomplished less than you would like . . . . .
- c. Didn't do work or other activities as carefully as usual . . . . .

	YES	NO
a.	1	2
b.	1	2
c.	1	2

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

- 1 Not at all
- 2 Slightly
- 3 Moderately
- 4 Quite a bit
- 5 Extremely

7. How much bodily pain have you had during the past 4 weeks? *(circle one number)*

1	None
2	Very mild
3	Mild
4	Moderate
5	Severe
6	Very severe

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

1	Not at all
2	Slightly
3	Moderately
4	Quite a bit
5	Extremely

9. These questions are about how you feel and how things have been with you during the past 4 weeks. For each question, 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)*

- a. Did you feel full of pep? .....
- b. Have you been a very nervous person? ..
- c. Have you felt so down in the dumps nothing could cheer you up? .....
- d. Have you felt calm and peaceful? .....
- e. Did you have a lot of energy? .....
- f. Have you felt downhearted and blue? ...
- g. Did you feel worn out? .....
- h. Have you been a happy person? .....
- i. Did you feel tired? .....

	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
1	2	3	4	5	6	
1	2	3	4	5	6	
1	2	3	4	5	6	
1	2	3	4	5	6	
1	2	3	4	5	6	
1	2	3	4	5	6	
1	2	3	4	5	6	
1	2	3	4	5	6	
1	2	3	4	5	6	
1	2	3	4	5	6	

10. 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.?)  
*(circle one number)*

- |   |                      |
|---|----------------------|
| 1 | All of the time      |
| 2 | Most of the time     |
| 3 | Some of the time     |
| 4 | A little of the time |
| 5 | None of the time     |

11. 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)*

- a. I seem to get sick a little easier than other people . . . . .
- b. I am as healthy as anybody I know . . . . .
- c. I expect my health to get worse . . . . .
- d. My health is excellent . . . . .

Definitely True	Mostly True	Not Sure	Mostly False	Definitely False
1	2	3	4	5
1	2	3	4	5
1	2	3	4	5
1	2	3	4	5

**B. AUA SYMPTOM INDEX**  
*(circle one number on each line)*

- 12. During the last month or so, how often have you had a sensation of not emptying your bladder completely after you finished urinating? . . . . .
- 13. During the last month or so, how often have you had to urinate again less than 2 hours after you finished urinating? . . . . .
- 14. During the last month or so, how often have you found you stopped and started again several times when you urinated? . . . . .
- 15. During the last month or so, how often have you found it difficult to postpone urination? . . . . .

Not at All	Less Than 1 Time in 5	Less than Half the Time	About Half the Time	More than Half the Time	Almost Always
0	1	2	3	4	5
0	1	2	3	4	5
0	1	2	3	4	5
0	1	2	3	4	5

	Not at All	Less Than 1 Time in 5	Less than Half the Time	About Half the Time	More than Half the Time	Almost Always
16. During the last month or so, how often have you have a weak urinary stream? . .	0	1	2	3	4	5
17. During the last month or so, how often have you had to push or strain to begin urination? . . . . .	0	1	2	3	4	5

	None	1 Time	2 Times	3 Times	4 Times	5 or More Times
18. During the last month, how many times did you most typically get up to urinate from the time you went to bed at night until the time you got up in the morning? . . . . .	0	1	2	3	4	5

**C. BOTHERSOME INDEX**

19. Overall, how bothersome has any trouble with urination been during the last month?  
*(circle one number)*

- |   |                       |
|---|-----------------------|
| 0 | Not at all bothersome |
| 1 | Bothers me a little   |
| 2 | Bothers me some       |
| 3 | Bothers me a lot      |

**D. PROSTATE SPECIFIC QUESTIONS**

URINE FLOW

20. In the past week did you: *(circle one number)*

- |   |   |
|---|---|
| 1 | Have total control 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 no control over your urine flow.   |
| 6 | I have an indwelling catheter.  |

21. In the past week have you used any of the following to prevent or protect you from being incontinent?  
(circle one number on each line)

	YES	NO
a. Worn a pad in underwear .....	1	2
b. Worn more than 1 pad per day in underwear .....	1	2
c. A clamp .....	1	2
d. A catheter device .....	1	2
e. Injection therapy .....	1	2
f. Used medications .....	1	2
g. Limited activity in order to be near a bathroom .....	1	2

21h. Bowel habits: Overall, how big a problem have your bowel habits been for you during the last month?  
(circle one number)

- |   |                    |
|---|--------------------|
| 1 | Big problem        |
| 2 | Moderate problem   |
| 3 | Small problem      |
| 4 | Very small problem |
| 5 | No problem         |

**ERECTION**

22. Please choose the answer that best describes your sexual capabilities. (circle one number)

- |   |  |
|---|--|
| 1 | I am able to have a normal erection and intercourse.                                     |
| 2 | I am able to have an erection that allows vaginal penetration but is weaker than normal. |
| 3 | I am able to have an erection that is of insufficient strength for vaginal penetration.  |
| 4 | I am unable to have an erection.   |

23. Have you had any sexual activity or intercourse during the past month?

	YES	NO
(circle one number)	1	2

a. If no, did this bother you?  
(circle one number)

- |   |               |
|---|---------------|
| 1 | Not at all    |
| 2 | Just a little |
| 3 | Some          |
| 4 | Fair amount   |
| 5 | A lot         |

If Yes to Question 23, please answer Questions 24, 25, and 26.

	Very High	High	Moderate	Low	Very Low
24. In the last <u>month</u> , I would rate my level of interest in sexual activities as: (circle one number) .....	1	2	3	4	5

	Very Good	Good	Moderate	Poor	Very Poor
25. In the last <u>month</u> , I would rate my sexual functioning as: (circle one number) .....	1	2	3	4	5

	Very Satisfied	Satisfied	Moderately Satisfied	Not Very Satisfied	Not Satisfied At All
26. In the last <u>month</u> , I would rate my satisfaction with my sexual functioning as: (circle one number) .....	1	2	3	4	5

**OVERALL HEALTH**

	Extremely Unpleasant	Unpleasant	Moderately Unpleasant	Slightly Unpleasant	Normal
27. Please score how you feel your life has been affected by the state of your health (any disease or treatment) during the past <u>week</u> . (circle one number)	1	2	3	4	5

(Circle one number on each line)

	A Lot	Some	Only a Little	None at All
28. How much physical discomfort would you say you have because of anything related to your prostate cancer or the effects of its treatments?	1	2	3	4
29. How much do you worry about your health because of anything related to your prostate cancer or the effects of its treatments?	1	2	3	4
30. How much would you say your day-to-day activities are limited by anything related to your prostate cancer or the effects of its treatment?	1	2	3	4
31. Overall, how much would you say you are bothered by anything related to your prostate cancer or the effects of its treatment?	1	2	3	4



32. Overall, how would you describe the way you feel about how your treatment has worked out?  
*(circle one number)*

Delighted	Pleased	Mostly Satisfied	Mixed	Mostly Dissatisfied	Unhappy	Terrible
1	2	3	4	5	6	7

33. How would you rate the medical care you received for prostate cancer?  
*(circle one number)*

Excellent	Very Good	Good	Fair	Poor
1	2	3	4	5

**VA/NCI COOPERATIVE STUDY #407 - PIVOT DEATH OR STUDY TERMINATION FORM 07**

Medical Center Name \_\_\_\_\_ VA Medical Center No. \_\_\_\_\_

NCI Institute No./Affiliate No. \_\_\_\_\_ / \_\_\_\_\_

NCI Group (1=CALGB, 2=ECOG, 3=SWOG) \_\_\_\_\_

Patient Name \_\_\_\_\_

Patient No. \_\_\_\_\_

Date Completed: Mo \_\_\_\_\_ Day \_\_\_\_\_ Yr \_\_\_\_\_

**1. REASON FOR TERMINATION** . . . . . \_\_\_\_\_

- 1=Study concluded
- 2=Patient died (complete Death Report below)
- 3=Patient withdrew, location known (date last seen is date of termination)
- 4=Lost to follow-up, location unknown
- 5=Other

**DEATH REPORT** (attach copy of autopsy report, death certificate, or discharge summary if available.)

2. Date of death . . . . . Mo \_\_\_\_\_ Day \_\_\_\_\_ Yr \_\_\_\_\_

3. Was autopsy performed? (1=Yes, 2=No) . . . . . \_\_\_\_\_

A. If Yes, did autopsy show evidence of CAP? (1=Yes, 2=No) . . . . . \_\_\_\_\_

IF YES:

B. Was disease locally confined? (1=Yes, 2=No) . . . . . \_\_\_\_\_

C. Was there pathologic evidence of metastatic CAP? (1=Yes, 2=No) . . . . . \_\_\_\_\_

**CAUSES OF DEATH** (use codes below to respond to each item):

**1=No; 2=Primary cause; 3=Contributory; 4=Possible; 5=Unknown**

4. Prostate cancer . . . . . \_\_\_\_\_

5. Cardiovascular . . . . . \_\_\_\_\_

6. Cerebrovascular . . . . . \_\_\_\_\_

7. Pulmonary . . . . . \_\_\_\_\_

8. Infectious . . . . . \_\_\_\_\_

9. Non-CAP cancer . . . . . \_\_\_\_\_

10. Suicide . . . . . \_\_\_\_\_

11. Accident . . . . . \_\_\_\_\_

12. Other, specify \_\_\_\_\_ . . . . . \_\_\_\_\_

**IF QUESTION 4 IS CODED "2", "3", OR "4", COMPLETE THE FOLLOWING:**

**1=YES**

**2=NO**

13. Toxicity from CAP related treatment . . . . . \_\_\_\_\_

14. Pre-operative evaluation for CAP surgery . . . . . \_\_\_\_\_

15. Morbid event occurring within 30 days after surgery . . . . . \_\_\_\_\_

16. Morbid event within 30 days after randomization to Expectant Management . . . . . \_\_\_\_\_

P.I.'s Signature \_\_\_\_\_

Medical Center Name \_\_\_\_\_ VA Medical Center No. \_\_\_\_\_

NCI Institute No./Affiliate No. \_\_\_\_\_/\_\_\_\_\_

NCI Group (1=CALGB, 2=ECOG, 3=SWOG) \_\_\_\_\_

Patient Name \_\_\_\_\_ Patient No. \_\_\_\_\_

Date Completed: Mo\_\_ Day\_\_ Yr\_\_

1. DATE OF BIOPSY/FINE NEEDLE ASPIRATION ..... Mo\_\_ Day\_\_ Yr\_\_

2. HISTOLOGIC GRADE .....

- 1=Well differentiated
- 2=Moderately well differentiated
- 3=Poorly differentiated/Undifferentiated
- 9=Unknown

3. GLEASON HISTOLOGIC GRADE

Gleason Score 1 .....

Gleason Score 2 .....

Gleason Sum (Score 1+2) .....

P.I.'s Signature \_\_\_\_\_

Medical Center Name \_\_\_\_\_ VA Medical Center No. \_\_\_\_\_  
 NCI Institute No./Affiliate No. \_\_\_\_\_ / \_\_\_\_\_  
 NCI Group (1=CALGB, 2=ECOG, 3=SWOG) \_\_\_\_\_  
 Patient Name \_\_\_\_\_ Patient No. \_\_\_\_\_  
 Date Completed: Mo \_\_\_\_ Day \_\_\_\_ Yr \_\_\_\_

1. Reason for Breach of Protocol . . . . . \_\_\_\_\_

- 1=Randomized to radical prostatectomy, surgery delayed . . . . . **Go to #2**  
 (>6 weeks after randomization or 3 months if receiving downstaging hormone therapy)
- 2=Randomized to radical prostatectomy, failure to have surgery . . . . . **Go to #3**
- 3=Randomized to expectant management, prostatectomy performed . . . . . **Go to #4**
- 4=Randomized to expectant management, definitive therapy or treatment  
 instituted for reasons other than symptomatic or metastatic  
 disease (including "early" hormone treatment) . . . . . **Go to #5**

2. A. Decision to delay was . . . . . \_\_\_\_\_

- 1=Patient initiated
- 2=Physician initiated
- 3=Other \_\_\_\_\_

B. Was delay due to intercurrent medical event (1=Yes, 2=No) . . . . . \_\_\_\_\_

3. A. Reason for no surgery . . . . . \_\_\_\_\_

- 1=Patient refusal
- 2=Physician recommendation
- 3=Other \_\_\_\_\_

B. Was cancellation of surgery due to new diagnosis of High Surgical Risk (1=Yes, 2=No) . . . . . \_\_\_\_\_

C. Treatment Plan for radical prostatectomy . . . . . \_\_\_\_\_

- 1=Rescheduled                      2=Postponed indefinitely

D. Type of initial treatment utilized . . . . . \_\_\_\_\_

- 1=Radiation Therapy              2=Cryotherapy
- 3=Hormonal Therapy              4=Expectant Management
- 5=Other \_\_\_\_\_

4. If radical prostatectomy was done, please complete:

**ALSO COMPLETE "SURGICAL FORM 03"**

A. Date of surgery ..... Mo\_\_ Day\_\_ Yr\_\_

B. Reason for surgery ..... \_\_\_\_\_

1=Patient initiated

2=Physician recommendation

3=Other \_\_\_\_\_

C. Where was surgery done ..... \_\_\_\_\_

1=VA

2=VA patient at other hospital

3=NCI patient at other than NCI hospital

5. For expectant management, if other therapy was done, describe intervention, date, location, and reason:

**ALSO COMPLETE "SUMMARY OF TREATMENT FOR CAP FORM 05"**

Intervention \_\_\_\_\_

Date: \_\_\_\_\_

Where was intervention done: \_\_\_\_\_

Reason for intervention: \_\_\_\_\_

P.I.'s Signature \_\_\_\_\_

**APPENDIX G**  
**PARTICIPATION**

## PARTICIPATION

Listed below are names of investigators who have expressed willingness to participate in CSP#407 as of July 6, 1993. Please note that this does not include many nonVA centers that will participate through the NCI Oncology Groups.

VA MEDICAL CENTERS		
ALBUQUERQUE, NM Dr. Powers	FORT HARRISON, MT Michael Agee	MILWAUKEE, WI Christopher Dixon
ANN ARBOR, MI Rodney Davis	FORT WAYNE, IN Christopher Steidle	OKLAHOMA CITY, OK William Parry
ASHEVILLE, NC Earl Shook	GAINESVILLE, FL Howard Epstein	PALO ALTO, CA John Kabalin
ATLANTA, GA Sam D. Graham	HAMPTON, VA Ali Farpour	PITTSBURGH, PA Raoul Salup
BAY PINES, FL Perry Hudson	HOUSTON, TX Dov Kadmon	PORTLAND, OR Thomas Klein
BIRMINGHAM, AL Donald A. Urban	INDIANAPOLIS, IN Richard Foster	PROVIDENCE, RI August Zabbo
BRONX, NY Vincent Ciavarra	IOWA CITY, IA Bernard Fallon	SAN ANTONIO, TX Thomas Ball
BROOKLYN, NY Arthur Crowley	KANSAS CITY, MO John D. Foret	SAN FRANCISCO, CA Perinchery Narayan
CASTLE POINT, NY Bok Lee	LEXINGTON, KY David P. Wood	SAN JUAN, PR Luis Baez Macso
CINCINNATI, OH Patrick O'Donnell	LITTLE ROCK, AR Michael J. Schutz	SEATTLE, WA William Ellis
CLARKSBURG, WV Unyime Nseyo	LOS ANGELES, CA Brent Trieeger	SHREVEPORT, LA Dan Culkin
COLUMBIA, MO Steven Weinstein	MADISON, WI Timothy Moon	SYRACUSE, NY Dennis Krauss
DALLAS, TX Claus G. Roehrborn	MANHATTEN, NY Pablo L. Torre	TAMPA, FL
DENVER, CO E.D. Crawford	MEMPHIS, TN Al Patterson	TEMPLE, TX Charles F. Johnson
DURHAM, NC Phillip J. Walther	MIAMI, FL Mark Salloway Arnon Krongrad	WEST ROXBURY, MA Joseph Jacobson Subbarao Yalla
EAST ORANGE, NJ Mitchell Bamberger		WHITE RIVER JUNCTION, VT Thomas Davis

**PARTICIPATION (Cont.)**

<b>NONVA CENTERS</b>	
<p><b>ANN ARBOR, MI</b> (University of Michigan) Rodney Davis</p>	<p><b>LEXINGTON, KY</b> (University of Kentucky) David P. Wood</p>
<p><b>ATLANTA, GA</b> (Emory University) Sam D. Graham</p>	<p><b>LOS ANGELES, CA</b> (UCLA) Brent Trieger</p>
<p><b>BIRMINGHAM, AL</b> (University of Alabama) Donald A. Urban</p>	<p><b>MADISON, WI</b> (University of Wisconsin) Timothy Moon</p>
<p><b>BRONX, NY</b> Vincent Ciavarra</p>	<p><b>MEMPHIS, TN</b> (University of Tennessee) Al Patterson</p>
<p><b>BROOKLYN, NY</b> Arthur Crowley</p>	<p><b>MILWAUKEE, WI</b> (University of Wisconsin) Christopher Dixon</p>
<p><b>BURLINGTON, VT</b> (University of Vermont) John Roberts</p>	<p><b>PITTSBURGH, PA</b> (University of Pittsburgh) Raoul Salup</p>
<p><b>CLARKSBURG, WV</b> (University of West Virginia) Unyime Nseyo</p>	<p><b>OAKLAND, CA</b> (Oakland Naval Hospital) Raymond Leidich</p>
<p><b>DALLAS, TX</b> (University of Texas) Claus G. Roehrborn</p>	<p><b>SAN FRANCISCO, CA</b> (University of California/San Francisco) Perinchery Narayan</p>
<p><b>DURHAM, NC</b> (Duke University) Phillip J. Walther</p>	<p><b>SEATTLE, WA</b> (University of Washington) William Ellis</p>
<p><b>FORT SAM HOUSTON, TX</b> (Brooke Army Medical Center) Ian Thompson</p>	<p><b>SHREVEPORT, LA</b> (Louisiana State) Dan Culkin</p>
<p><b>GAINESVILLE, FL</b> (University of Florida) Howard Epstein</p>	<p><b>TRIPLER AMC, HI</b> (Tripler Army Medical Center) Steven Gange</p>
<p><b>HOUSTON, TX</b> (Baylor College of Medicine) Peter Scardino</p>	
<p><b>IOWA CITY, IA</b> (University of Iowa) Bernard Fallon</p>	



**VA COOPERATIVE STUDY 407**

**"PROSTATE CANCER INTERVENTION VERSUS OBSERVATION TRIAL (PIVOT):  
A RANDOMIZED TRIAL COMPARING RADICAL PROSTATECTOMY VERSUS  
PALLIATIVE EXPECTANT MANAGEMENT FOR THE TREATMENT OF  
CLINICALLY LOCALIZED PROSTATE CANCER"**

**PLANNING COMMITTEE**

Timothy J. Wilt, M.D., M.P.H., Minneapolis VAMC (Co-Chairman)

Michael K. Brawer, M.D., Chief, Section of Urology, Seattle VAMC (Co-Chairman)

Richard Kaplan, M.D., Senior Scientist, CTEP, National Cancer Institute

Michael Barry, M.D., Director, Ambulatory Care Program, Harvard Medical School

Timothy Moon, M.D. Chief, Urology , Madison VAMC

Perinchery Narayan, M.D., Chief, Urology, San Francisco VAMC

Peter Scardino, M.D. Chief, Urology, Baylor College of Medicine

Ian Thompson, M.D., Chief, Urology, Brook Army Medical Center

John Wasson, M.D., Community and Family Medicine, Dartmouth Medical School

Thomas Wheeler, M.D., Pathology, The Methodist Medical Center, Baylor School of Medicine

Joseph Collins, Sc.D., Chief, CSPCC, Perry Point VAMC

David Weiss, Ph.D., Study Biostatistician, Perry Point VAMC

**- PRIVILEGED AND CONFIDENTIAL -**

Not to be Disseminated Beyond its Official

Committee Function and Use

August, 1993

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DEPARTMENT OF VETERANS AFFAIRS  
Medical Center  
Perry Point MD 21902

August 5, 1993

In Reply Refer To: 641/151E  
CSP #93/407

Daniel Deykin, M.D.  
Chief, Cooperative Studies Program (151-I)  
VA Medical Center  
150 South Huntington Avenue  
Boston, MA 02130

Dear Dr. Deykin:

The Planning Committee and I agree that VA Cooperative Study #407, "Prostate Cancer Intervention Versus Observation Trial (PIVOT): A Randomized Trial Comparing Radical Prostatectomy Versus Palliative Expectant Management for the Treatment of Clinically Localized Prostate Cancer," is ready for submission to the Cooperative Studies Evaluation Committee. There are a few issues that I feel need to be brought to the attention of CSEC. Most of these issues are related in some way to the funding of the study. The first issue that I feel that CSEC should be aware of is the fact that the study will be jointly funded by the VA and the National Cancer Institute (NCI). Although the study was originally proposed as a VA cooperative study, the large number of centers required (80) made it necessary to seek non-VA centers and support. Thus, the Principal Proponent's have approached NCI about a collaboration. Since neither the VA nor NCI would be able to do the study by themselves, a joint effort is being proposed. The VA intends to identify 45 participating centers with NCI identifying 30-40 centers.

The current agreement with NCI is that the VA will fund the VA centers and that NCI will fund the non-VA centers. Data management and statistical support would be provided by the Perry Point CSPCC. Other support for the study, such as the Chairman's Office and the study's central PSA laboratory, is currently in the VA budget. However, as the letter of support from the NCI Project Office (see Appendix D) indicates, there is a possibility that NCI will make additional funds available for the study. This will have to be worked out in the upcoming months.

The second issue that I feel needs to be brought to the attention of CSEC is how the VA participating centers will be funded. Unlike the vast majority of VA cooperative studies that place a study assistant at each participating center, in this study, investigators will be given funds based on the amount of work that they do. They will be given \$1,000 for each patient randomized, \$400 to \$500 for each patient in follow-up each year, \$50 for each patient who watches the study's videotape, and \$150 for each monthly patient screening log that they complete. This model of funding has been successfully applied in the DIG Study (CS #995, "Trial to Evaluate the Effect of Digitalis on Mortality in Heart Failure [VA-NHLBI])" that is coordinated at the Perry Point CSPCC. I believe that this funding model can also be successfully applied to this study because the study procedures and forms have been kept simple. Even with this funding model, the total cost for the VA portion of the study will be about \$15.5 million. These costs will be spread over 16 years, however. The highest costs (about \$4.2 million) will occur during the first three years when recruitment is taking place.

Daniel Deykin, M.D.

2.  
August 5, 1993

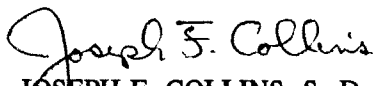
A third issue that I would like to address is the beyond core costs for the CSPCC. The CSPCC is requesting two FTE over the course of the study. We have never requested additional personnel before. We will need a Project Manager and an additional Computer Assistant. With the coordination and data management of 80 potential sites including dealings with the various NCI coordinating centers, it is essential that there be a dedicated person to handle administrative and protocol aspects of the study and one to handle the data management aspects. Having such staff has been extremely important for both the DIG Study (CS #995) and our studies with the National Institute on Drug Abuse (CS #999 studies). With our current workload, it would not be possible to use my core staff for these tasks. However, this will be monitored over the course of the study and any vacancies during the course of the study will only be filled if needed.

A fourth issue which also concerns the budget is that the cost of the PSA kits is included in the central laboratory budget. There is a good possibility that these kits will be donated by the manufacturer (Abbott). If the kits are donated, then the costs for the central laboratory will be reduced by over \$700,000.

The study itself is one that I believe is very important and very timely. There has been a push lately in prostate cancer, as well as all cancers, to develop screening tests that will enable the earliest detection possible of the cancer. On the other hand, there have been recent articles questioning the value of early intervention in prostate cancer because the cancer is slow growing for the most part and the risk of intervention may be worse than the disease if quality life expectancy is not increased. Thus, it is also a study where a valuable result is obtained no matter what the outcome. If early intervention is shown to improve quality life expectancy, then thousands of lives could be lengthened by the early detection and treatment of cancer. However, if early intervention does not improve quality life expectancy, then huge cost savings could be achieved by not providing screening and treatment for early prostate cancer and thousands of men each year will not be subjected to the risks and morbidity involved with the early treatment. The letter of support from the NCI Project Officer in Appendix D of the proposal indicates that the NCI also considers this study to be very important.

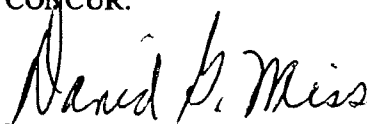
While the Co-Principal Proponents are relatively young (which is an advantage in a 16-year study), they both have been involved extensively in research and both have been investigators in other VA cooperative studies. I believe that both Proponents are highly capable and, if CSEC were to approve the study, there is a high probability that the study would be successfully completed.

Sincerely,

  
JOSEPH F. COLLINS, Sc.D.  
Chief, Cooperative Studies  
Program Coordinating Center

---

CONCUR:

  
DAVID G. WEISS, Ph.D.

## ABSTRACT

Cancer of the prostate (CAP) is the most common nondermatologic cancer and the second most frequent cause of cancer deaths in men. Cure is currently not possible for disseminated disease. Cancer confined to the prostate is believed to be curable, with the most frequently recommended therapy being surgical extirpation of the tumor with radical prostatectomy. However, despite increasing cancer detection and surgical treatment, population-based mortality rates from prostate cancer have not decreased nationally nor in states with high rates of radical prostatectomy. Existing evidence has not clearly demonstrated the therapeutic benefit of radical prostatectomy compared to expectant management in the treatment of localized prostate cancer. Data from case series, structured review of the medical literature and a decision analysis model suggest that either treatment approach provides equivalent all-cause and prostate cancer specific mortality as well as quality-adjusted life expectancy.

While radical prostatectomy provides potentially curative removal of the cancer, it subjects patients to the morbidity and mortality of surgery which may be neither necessary nor effective. Expectant management does not offer complete removal of cancer which may result in development of symptoms or metastatic progression. However, it provides palliative therapy and avoids potentially excessive and morbid interventions in asymptomatic patients.

Screening programs have been advocated to detect CAP while it is still localized in hope that cure is possible. Before early detection programs can rationally be implemented, the following question must first be answered: does early treatment of clinically localized prostate cancer with radical prostatectomy reduce all-cause and prostate cancer specific mortality and morbidity compared to expectant management? The primary objective of our proposed study is to determine which of two strategies is superior for the management of clinically localized CAP: 1) radical prostatectomy with early intervention for disease persistence or recurrence or 2) expectant management with reservation of therapy for palliative treatment of symptomatic or metastatic disease progression.

- Size and Duration: 2000 patients; 80 medical centers (VA and NCI); 15 years (3 years intake, 12 years follow-up)
- Inclusion Criteria:
1. Age  $\leq$  75
  2. T1 or T2, NX, MO adenocarcinoma of the prostate (all histologic grades)
- Exclusion Criteria:
1. Coexisting medical conditions expected to result in a life expectancy  $<$  10 years (e.g., severe cardiac, pulmonary, liver or renal disease)
  2. Prior therapy for prostate cancer
  3. Evidence of nonlocalized disease including:
    - a) PSA  $>$  100
    - b) Bone scan consistent with prostate cancer
    - c) Other imaging/lab studies indicating nonlocalized prostate cancer
  4. Current use of estrogens, androgen blocking drugs, or finasteride
- Patient Recruitment: From urology, general medical, oncology or community screening clinics; CAP support groups; pathology, laboratory, ultrasound logs indicating prostate cancer or elevated PSA. Use of patient and family educational videotapes and written materials.
- Randomized Rx Arms:
- \* Radical prostatectomy, plus intervention for evidence of disease persistence or recurrence.
  - \* Expectant management with palliative therapy reserved for symptomatic or metastatic disease progression.
- Follow-Up Visits: Schedule of Visits: 6 weeks following randomization, every 3 months the first year and every 6 months until the end of the trial (minimum 12 years; maximum 15 years).
- Visit Protocols: Every visit: Digital rectal examination, urologic symptoms, prostate cancer quality of life questionnaires, PSA, PAP. Annual visit: Bone scan, serologic samples for central laboratory.
- Laboratory: Local Laboratory: Pathologic and histologic diagnosis of prostate cancer, PSA. Central Laboratory: Tissue specimen samples for confirmation, tissue and serum bank for special studies and PSA assays.
- End Points: Primary: All cause mortality. Secondary: Prostate cancer specific mortality and morbidity, quality of life, morphologic, histologic, laboratory and demographic predictors of outcomes.





## I. INTRODUCTION

Cancer of the prostate (CAP) is the most common nondermatologic cancer and the second most frequent cause of cancer deaths in men (1). Cure is currently not possible for disseminated disease. Cancer confined to the prostate is believed to be curable, with the most frequently recommended therapy being surgical extirpation of the tumor with radical prostatectomy. However, despite increasing cancer detection and surgical treatment, population-based mortality rates from prostate cancer have not decreased nationally nor in states with high rates of radical prostatectomy.

Existing evidence has not clearly demonstrated the therapeutic benefit of radical prostatectomy compared to expectant management in the treatment of localized prostate cancer (2). Data from case series, structured review of the medical literature and a decision analysis model suggest that either treatment approach provides equivalent all-cause and prostate cancer specific mortality as well as quality-adjusted life expectancy (3-8). The only randomized trial was limited by small sample size and incomplete clinical staging. However, the results showed no difference between prostatectomy and expectant management (9). Recent information in the medical and lay press has resulted in an increased interest and heightened controversy regarding management of clinically localized prostate cancer (10-15).

Radical prostatectomy provides potentially curative removal of the cancer. However, radical prostatectomy subjects patients to the morbidity and mortality of the surgery and may be neither necessary nor effective. Expectant management does not offer complete removal of cancer. Patients may develop symptomatic or metastatic progression that was previously localized. However, it provides palliative therapy if there is symptomatic or metastatic disease progression. Furthermore, expectant management avoids potentially excessive and morbid interventions in asymptomatic patients, and emphasizes management approaches that focus on relieving symptoms while minimizing therapeutic complications.

Screening programs have been advocated to detect CAP while it is still localized in hope that cure is possible. Before early detection programs can rationally be implemented the following question must first be answered: does early treatment of clinically localized prostate cancer with radical

prostatectomy reduce all-cause and prostate cancer specific mortality and morbidity compared to expectant management?

The primary objective of our proposed study is to determine which of two strategies is superior for the management of clinically localized CAP: 1) radical prostatectomy with early intervention for disease persistence or recurrence or 2) expectant management with reservation of therapy for palliative treatment of symptomatic or metastatic disease progression. Outcomes will include total mortality, CAP mortality, disease free and progression free survival, morbidity and quality of life.

This objective will be achieved by conducting a randomized controlled trial in 2000 men with clinically localized prostate cancer at 45 VA Medical Centers through the VA Cooperative Studies Program and at 35 private medical centers through the National Cancer Institute.

## **II. BACKGROUND AND RATIONALE**

### **A. Epidemiology**

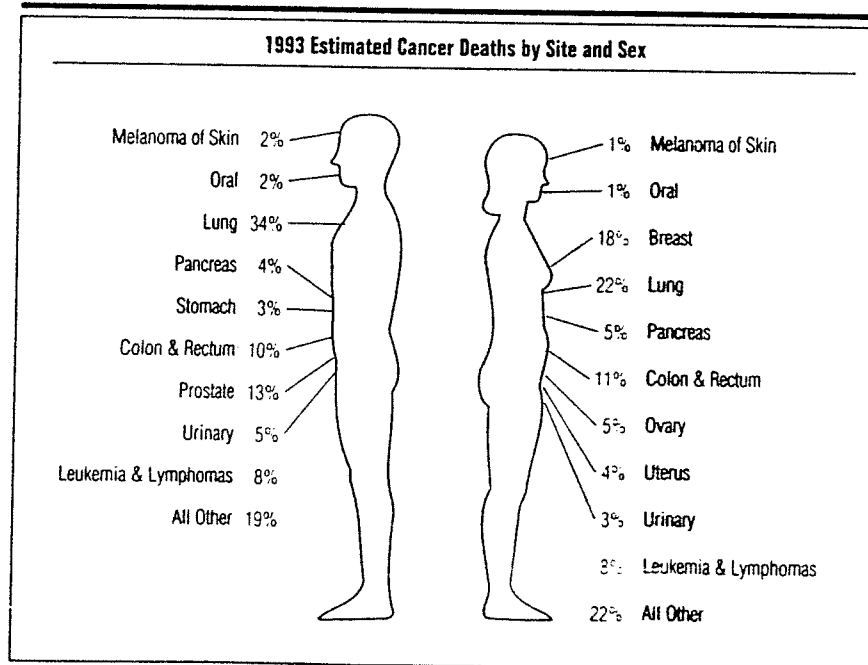
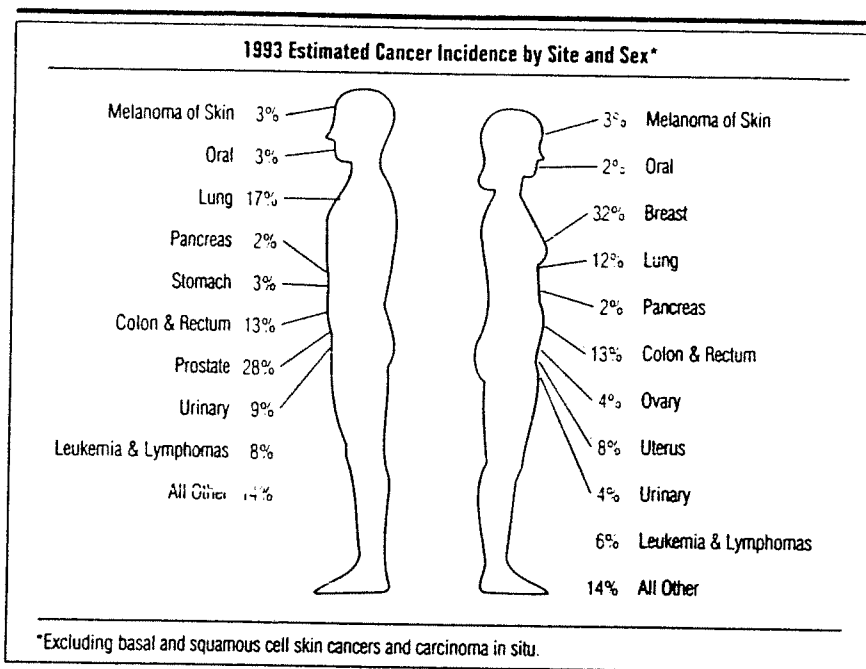
Cancer of the prostate is the most frequently diagnosed nondermatologic cancer and the second leading cause of cancer related mortality (Figure 1). In 1993 it is estimated that 165,000 cases of CAP will be diagnosed and 35,000 men will die due to prostate cancer(1). Age adjusted incidence rates of CAP have risen over the last decade for both white and black men (8% and 30% respectively). During those years, the death rates increased 7.5% in white men and 5.9% in blacks. CAP increases with age, with the risk of disease rising sharply above 50. The median age at diagnosis is 72 years. In addition to age, suspected or known risk factors for the development of prostate cancer include a family history of prostate cancer, black race, and smoking history.

Continued improvements in life expectancy and a shift in the age distribution in favor of an older population will increase the number of patients with and dying of prostate cancer. Additionally, newer early CAP detection methods used in large scale screening and case detection programs (e.g. prostate specific antigen [PSA] and transrectal ultrasound [TRUS]) will increase the number of clinically detected prostate cancers that previously remained undiagnosed. The increased detection of prostate cancer has been paralleled by an increase in the treatment modalities provided. In

FIGURE 1

1993 Estimated Cancer Incidence (Top)  
and Deaths (Bottom) by Site and Sex

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particular, the rate of radical prostatectomies has risen almost six fold from 1987-1992 (Figure 2). Despite the marked increased utilization of radical prostatectomy and radiation therapy for clinically localized prostate cancer, death from prostate cancer has not been reduced (Figure 3). This suggests that current methods utilized for early therapy of clinically localized prostate cancer may not be optimal.

Biologically, the concept of surgical cure is based on the assumption that prostate cancer does not metastasize until after it has become clinically detectable. Radical prostatectomy series indicate excellent disease free and overall survival especially in patients with clinically detectable small volume (T1) and well differentiated (Gleason 1-3) tumors. Surgery theoretically offers potential cure in these patients. However, small, well differentiated prostate cancers tend to grow slowly. Observational studies indicate that most of these patients die of causes unrelated to their prostate cancer. Therefore, early detection and subsequent surgical intervention in these individuals may result in unnecessary evaluations, anxiety, and risk.

Conversely, patients with large volume or poorly differentiated CAP have a high probability of pathologically confirmed disseminated disease or develop cancer recurrence despite apparent complete extirpation by radical prostatectomy. Therefore, while these patients have a poor 10 year survival with expectant management they also are unlikely to be cured by surgery. Even in patients with pathologically defined localized disease, CAP recurrence at 10 years has been demonstrated in up to 40% of patients having a radical prostatectomy (9, 16-22). Furthermore, 20% of these patients die from their prostate cancer despite undergoing radical prostatectomy. These patients therefore, have been exposed to the morbidity and mortality of a noncurative surgical procedure. It is possible, however, that if patients with this type of cancer were detected earlier and received prostatectomy that they may be cured of their prostate cancer.

Only one study has compared the outcomes of patients receiving radical prostatectomy with those allocated to expectant management (9). In the VACURG 2 study, there was no difference in survival at 15 years between the prostatectomy and expectant management group. The results of this study are limited by small sample size, incomplete clinical staging and uneven randomization of poorly differentiated cancers.

Figure 2 Time Trends of Radical Prostatectomy among Male Medicare Beneficiaries

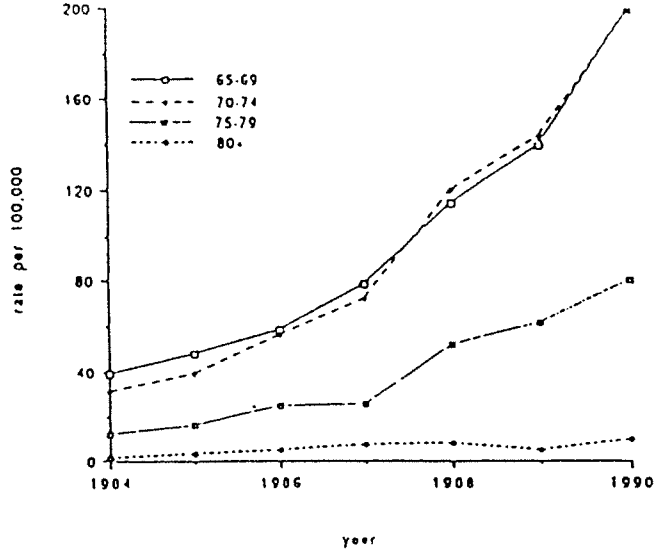
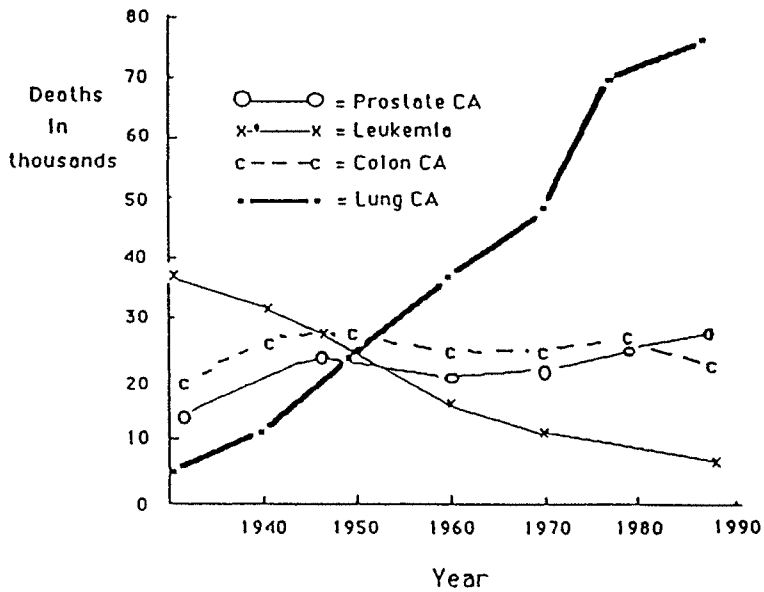


Figure 3: Age adjusted Cancer death rates (1930-1980)



B. Natural History and Expectant Management of CAP

Because of the high prevalence of cancer in the prostate found at autopsy of men who die of other causes, the slow progression rate of the tumor, the advanced age and comorbid conditions at diagnosis, patients with CAP are said to be more likely to die *with* rather than *from* their disease. Estimates from autopsy studies indicate that 30% of men over the age of 50 have prostate cancer but that only 1 in 200 men with carcinoma of the prostate will die from their disease. Approximately 10% of men over 50 years will have progression of CAP so that it is clinically detectable or causes symptoms. In these patients, the mortality rate increases to one in four (23).

Early CAP detection and treatment programs presume that treatment with radical prostatectomy prolongs survival in subjects with clinically localized CAP. This presumption is not convincingly supported by results from observational studies, case series, structured review of the medical literature, a decision analysis model and a small clinical trial (Tables 1 and 2) (3-5, 9-22, 24). These studies demonstrate that the therapeutic approach of expectant management and palliative therapy reserved for symptomatic or metastatic disease progression provides similar 10- year survival rates and quality-adjusted life expectancy compared to radical prostatectomy.

**Table 1: Results of Five Studies of Observation for Clinically Localized CAP**

Author (Ref)	Number Patients	Follow-up Years	Overall Mortality (%)	CAP Mortality (%)	CAP Progression (% Includes CAP Death)
Johansson (3)	223	10.2	56	8	34
Whitmore (4)	75	9.5	39	15	69
Hanash (24)	179	15	55	45	NA
George (5)	120	7	44	4	83
Madsen (9)	50	10	52	6	18

Expectant management is generally recommended for clinically localized CAP in Europe. This approach is believed to provide equal long-term survival to prostatectomy and avoid operative morbidity and mortality (3-5, 9, 24). In the United States, expectant management is the treatment modality employed in 66% of Stage A and 17% of Stage B CAP patients. Morbidity due to progression

of disease has generally been successfully treated with hormone manipulation and conservative urologic procedures. Thus, prevention or treatment of symptoms from the primary tumor is not an important indication for radical prostatectomy (3).

A structured review of the medical literature revealed that the mean age of patients treated by expectant management was 71 years, 7% had poorly differentiated CAP, and the median annual all-cause and prostate cancer specific mortality rates were 0.060 (95% CI = 0.050-0.104) and 0.009 (0.006-0.012) respectively (12).

### C. Surgical Treatment of CAP

The principal basis for support of surgical treatment for CAP is the superior 10-year survival rates in individuals with localized disease compared to those with metastatic prostate cancer. The 10-year survival in patients with metastatic disease is less than 15%. In comparison, the 10-year overall and prostate cancer specific survival in patients with clinically localized CAP receiving radical prostatectomy are approximately 55% and 85% respectively (Table 2) (9, 16-22). This difference is often interpreted to mean that if prostate cancer is found "early" enough, it can be excised before it metastasizes, resulting in the patient being "cured" of an otherwise fatal disease. This interpretation does not take into account the problems of lead-time and length (or susceptibility) bias in which an apparent benefit of treatment spuriously results from preferentially selecting patients with early or indolent disease and then comparing them with others not so selected.



**Table 2: Results from Studies of Radical Prostatectomy for Localized CAP**

Author (Ref)	Number Patients	Total Mortality Rate: %		CAP Mortality %	CAP Progression: (% Includes CAP Death)
		5-Year	10-Year		
Berlin (16)	143	20	48	NA	NA
Kopecky (17)	73	27	50	NA	NA
Belt (18)	185	22	45	8	14
Belt (18)	267	35	60	19	40
Veenema (19)	159	16	48	8	NA
Correa (20)	67	8	27	5	24
Madsen (9)	61	22	57	4	15
Smith (21)	186	NA	40	22	35
Box (22)	212	18	37	NA	NA

Complication rates of surgical therapy vary with the surgeon and technique utilized. These include a perioperative mortality of (0.5-2%), urinary incontinence (0-30%), vesicourethral stricture (12%), impotence (25-95%) and rectal injury requiring colostomy (1-3%) (12).

In the structured literature review by Wasson, the average age of patients treated with radical prostatectomy was 63 years, 11% had poorly differentiated CAP, the median annual all-cause and cancer-specific death rates were 0.032 (95% CI = 0.020-0.044) and 0.052 per patient year (95% CI = 0.009-0.015) respectively (12).

#### D. Radiation Treatment of CAP

Radical prostatectomy is the most frequently recommended intervention for patients with clinically localized CAP. Radiation therapy is also believed by some to provide comparable survival to radical prostatectomy in these patients (25-27). However, comparison of radiotherapy results with those of surgery is difficult. Radiotherapy series report outcomes on the basis of clinical staging. Surgical series frequently exclude the subset of patients with clinical Stage T1 and T2 disease found to have

metastatic nodal disease or extracapsular extension during surgery. Ten-year follow-up on patients having radiotherapy for clinically localized CAP is limited but indicate an overall survival of 45%.

A VA Oncology Group cooperative trial has provided evidence that patients treated with radiation had a higher rate of disease recurrence than patients treated with prostatectomy (28). Therefore, radiation therapy is generally reserved for patients judged to be poor surgical candidates or to have disease extending beyond the prostate gland (25-27). A prospective randomized trial, Southwest Oncology Group [SWOG #8890], was initiated comparing external beam irradiation with radical prostatectomy for clinical Stage A and B disease (29). This trial was discontinued because of low patient recruitment. Complications from radiation are similar to prostatectomy and include incontinence, impotence and rectal injury requiring colostomy.

The structured literature review of Wasson indicates that the mean age of patients treated with radiation therapy is 66 years, 21% have poorly differentiated CAP, and the median annual all-cause and prostate cancer specific mortality is 0.045 (95% CI = 0.040-0.052) and 0.023 (95% CI = 0.10-0.095) respectively (12).

While a trial comparing expectant management to prostatectomy and radiation therapy would be of great interest, we have elected not to include radiation therapy as a third treatment arm because of study cost, feasibility and sample size. Prior to randomization, patients will be informed about radiation therapy as a therapeutic option if they decline to enter this study.

#### E. Summary of Efficacy of Current Treatment Options

Drawing definitive conclusions regarding treatment efficacy from case series and the small clinical trials is difficult because of the variability in patient characteristics as well as differences in CAP stage and grade. These limitations were pointed out by Wasson and colleagues(12). They performed a structured literature review to define the clinical course of localized prostate cancer, the effectiveness of radical surgery and radiation therapy, and treatment complications. Because of methodological inadequacies of the available literature such as failure to stratify by grade of malignancy, extent of disease at the time of treatment and patient age as well as neglecting to identify patients lost to follow-up they concluded that "it is impossible for patients and their counselling physicians to make

informed choices based on knowledge of the benefits of radical prostatectomy, radiation or watchful waiting" (12).

A recent report utilized a decision analysis approach to assess outcomes from radiation, prostatectomy and expectant management for clinically localized prostate cancer (11). Their results demonstrate that even under optimistic assumptions the benefits of radical prostatectomy or radiation therapy are small. However, the efficacy varies depending upon assumptions of estimated interventional treatment efficacy and tumor metastatic rate. The authors state that "the only way to resolve the question of effectiveness [prostatectomy, radiation, or expectant management] is to obtain data on comparable patients by means of a sufficiently large clinical trial" (11). Until such a trial is completed they recommend that therapeutic choices should be based on interventional morbidity and patient preferences.

In summary, the results of these studies suggest that therapy reserved for palliative relief of symptomatic disease progression provides equivalent survival rates and quality adjusted life years to early intervention with prostatectomy or radiation. The uncertainty around these estimates indicate that a randomized trial comparing prostatectomy to expectant management is necessary to accurately determine the preferred strategy.

Prostatectomy offers the potential for complete removal of cancer. However, this intervention may be neither successful nor necessary. Expectant management, while not removing prostate cancer, avoids the morbidity and mortality from early intervention. Palliative therapy for symptomatic local disease progression with hormone manipulation and conservative urologic procedures has generally been successful. Thus, prevention or treatment of symptoms from the primary tumor is not an important indication for early intervention. While not commonly utilized in the United States, expectant management is frequently recommended for localized CAP in Europe.

Therefore, in 1993 the principal issue in prostate cancer remains the following unanswered question: is treatment necessary in whom it is possible and is treatment possible in whom it is necessary? The answer to this question requires the conduct of randomized controlled trials.

#### F. Comparison with Concurrent Studies

There are currently two randomized clinical trials investigating early interventional therapy versus expectant management for clinically localized CAP. A Danish study is comparing radiation treatment with expectant management. This study began in 1989, and has a projected sample size of 162 (30). The Swedish Oncologic Group is conducting a randomized clinical trial of lymph node dissection with subsequent prostatectomy if node negative versus expectant management (31). This study began in 1989 and has currently enrolled 220 patients with a projected sample size of 540. This study is only enrolling subjects with well differentiated CAP; i.e. those who will be less likely to develop disease progression with expectant management. Therefore, this smaller study is more likely to conclude that radical prostatectomy is of no benefit in clinically localized CAP. These studies lack sufficient power to detect a 40% increase in median overall survival or a 60% increase in prostate cancer specific survival from radiation or surgical therapy compared to expectant management. Additionally, surgical and radiation techniques used in Scandinavia are different than in the United States. Generalization of their results to patients in the United States will be difficult.

#### G. Screening Studies

The American Cancer Society-National Prostate Cancer Detection Project (ACS-NPCDP) is a multicenter, multidisciplinary study evaluating the use of transrectal ultrasound (TRUS), digital rectal examination (DRE), and prostatic specific antigen (PSA) for early detection of CAP in a large cohort of men not previously suspected of having prostate cancer (32). It does not have all-cause or prostate cancer specific mortality as primary outcome measures nor is this study of sufficient size to determine this outcome.

The National Cancer Institute Prostate, Lung, Colon, Ovarian Cancer Screening (PLCO) Project is a large multicenter trial being developed to investigate the effectiveness of DRE and PSA testing in the early detection and outcome of patients with prostate cancer (33). This study is designed to determine if early detection reduces mortality. Results from the PLCO project are unlikely to conclusively demonstrate that prostatectomy is superior to expectant management for localized CAP for the following reasons: 1) Patients not randomized to screening are likely to receive intermittent rectal examinations and PSA testing by their primary physician. This will dilute an expected benefit in the

screened group. A negative study might lead to the conclusion that screening and treatment with prostatectomy for CAP was of no benefit when one truly exists. 2) A positive study could not exclude a co-treatment effect as the reason for the improved survival in the screened group, (i.e. Patients screened for CAP are more likely to have medical therapy prescribed for comorbid conditions than patients not screened). 3) Results from the PLCO project will likely be confounded by lead and length time bias. Such bias is difficult to control for in screening studies and will make results susceptible to criticism. 4) Treatment of patients with localized prostate cancer detected in this study is not randomly assigned nor mandated. Conclusions regarding the efficacy of early intervention will thus be difficult. Therefore, a clinical trial comparing prostatectomy versus expectant management is necessary in addition to the current screening proposals.

### **III. STUDY HYPOTHESIS AND PRIMARY ENDPOINT**

The proposed study is a randomized clinical trial in patients with clinically localized prostate cancer designed to determine which of two treatment strategies is superior in reducing all-cause mortality: 1) radical prostatectomy and early intervention of subsequent disease persistence or recurrence or 2) expectant management with reservation of therapy for palliative treatment of symptomatic or metastatic disease progression.

### **IV. IMPORTANCE TO THE VA AND NCI**

Cancer of the prostate is the most frequently diagnosed cancer and the second leading cause of cancer related mortality. In 1993 it is estimated that 165,000 cases of CAP will be diagnosed and 35,000 men will die due prostate cancer. Because of continued improvements in life expectancy and a shift in the age distribution in favor of an older population, it has been estimated that, between the early 1980's and the year 2000, there will be a 37% increase in the number of prostate cancer-related deaths and a 90% increase in the number of cases of prostate cancer detected (34).

The growing magnitude of this health problem has heightened interest among patients, health care providers, and legislators in determining the preferred treatment for prostate cancer. Autopsy studies suggest a 30% prevalence of prostate cancer in the 28 million men 50 years of age or older. Thus, potentially 8.4 million men have prostate cancer. This undoubtedly overestimates the number of tumors

that will become clinically significant but reflects the potential disease burden if aggressive screening and treatment strategies are implemented.

A recent report addressing time trends, geographic variation and outcomes in Medicare patients having a radical prostatectomy for CAP indicated nearly a six-fold increase in the number of procedures performed since 1984. The American College of Surgeons Commission on Cancer compared the distribution of treatment modalities in patients with clinically localized prostate cancer in 1984 and 1990. Their findings confirmed the marked increase in the number of patients screened for prostate cancer and being offered early intervention. From a sample of 23,000 patients with newly diagnosed prostate cancer, treatment with radical prostatectomy in 1990 increased over threefold to almost five thousand (35). Therefore, it can be estimated that over 30,000 radical prostatectomy procedures are performed each year in the 165,000 patients with newly diagnosed prostate cancer. These statistics are not meant to imply that prostatectomy procedures are done inappropriately. Rather, they emphasize the growing utilization of radical prostatectomy, the impact this disease and its treatment have on United States health care, and the critical importance of conducting our clinical trial to be able to determine whether prostatectomy is superior to expectant management in patients with clinically localized CAP.

Recently, increased interest in CAP detection and treatment has developed in both the VA and NCI. The current PLCO screening study is sponsored by the NCI. It will provide valuable information on the effectiveness of early detection of prostate cancer. However, our clinical trial is necessary to determine whether subsequent intervention with radical prostatectomy provides improved survival in comparison to expectant management. Despite the large population of men at high risk for CAP served by the VA, the VA Preventive Medicine Program does not currently include prostate cancer screening because of the lack of available evidence that early detection and treatment is beneficial (36). Our study will provide evidence on the efficacy of early treatment of prostate cancer.

If the prevalence of CAP in the 8.6 million male veterans aged 50-70 is the same as reported in the screening studies of unselected men, then more than 2.3 million cases of CAP exist in this population (37). Presuming radical prostatectomy is performed in localized CAP, 891,000 veterans (248,000 Stage A2 and 643,000 Stage B tumors) would be potential candidates for radical prostatectomy. On a national level, a recent analysis estimated that the initial yearly cost for a national CAP screening and treatment program would range from \$4 to \$32 billion (38). This is between 0.5-6%

of the total United States' health care budget. Applying these screening and treatment cost estimates results in a potential yearly cost to the VA of \$1.8-\$13 billion.

Before widespread implementation of early detection programs can be advocated, it is critical to determine if treatment of localized CAP with radical prostatectomy improves survival. Our study will provide this information. If radical prostatectomy provides curative therapy in clinically localized CAP, then a large group of men with CAP would benefit from early detection and surgical treatment. Current recommendations from consensus panels, practice styles of primary care physician, and attitudes of patient will have to be modified to emphasize the importance of early detection and surgical referral for CAP. However, if expectant management provides equal or improved survival and quality of life, then many men are being subjected unnecessarily to screening and surgery with its attendant morbidity, mortality and cost.

## **V. RATIONALE FOR CHOICE OF POPULATION**

Our study is designed to enroll participants who are representative of patients in whom radical prostatectomy is generally performed. Prostatectomy is not routinely recommended in patients with a life expectancy less than 10 years. We have chosen an upper age limit of 75 because the median life expectancy of a 75-year old man is approximately 10 years.

We have included patients with clinical T1-T2 adenocarcinoma of the prostate regardless of histologic grading. Patients with clinically determined T1 and T2 tumors are believed to have localized prostate cancer and to be ideal candidates for surgical removal of the tumor. Patients with well differentiated prostate cancer have a low disease specific morbidity and mortality with expectant therapy. However, prostatectomy is also most likely to successfully remove the cancer in these individuals. Patients with poorly differentiated CAP have a high 10-year mortality rate regardless of treatment approach. The preferred therapeutic strategy in all of these patients is controversial and necessitates our clinical trial for definitive answers. We anticipate that approximately 10% of participants enrolled in this study will have poorly differentiated CAP. This is consistent with previous reports from case series of patients treated with radical prostatectomy or expectant management.

## VI. RATIONALE FOR STUDY DESIGN

Conclusions from previous studies are confounded by the small sample size, lack of control groups, the variability in tumor grade and stage, and patient populations enrolled. The potential benefit of either treatment strategy is large, however, because of the high prevalence of CAP. To avoid the limitations of previous studies, a randomized trial of prostatectomy versus expectant management is not only ethical but necessary in patients with clinical T1 and T2 disease. If prostatectomy is a treatment with even modest benefit, it could be valuable for patients with CAP, given the magnitude of the disease and the lack of effective therapy. It would be useful to know the magnitude of this benefit, in which patients it occurred, and what early detection strategies were most useful. However, if expectant management was shown to provide equivalent long-term survival and quality adjusted life-years, the associated morbidity and mortality of early intervention could be eliminated.

The study is designed to compare the current clinical practice strategy of radical prostatectomy with follow-up intervention for evidence of disease recurrence or persistence to an expectant management approach that reserves therapy for palliative relief of symptomatic or metastatic disease progression. The expectant management approach has as an emphasis minimization of therapeutic side effects. With increasing utilization of prostate cancer detection and treatment strategies, it is essential to determine if early detection and intervention with radical prostatectomy is effective.

We have chosen all-cause mortality as the primary outcome measure. The rationale for this decision is two-fold: 1) All-cause mortality is an unbiased and more easily defined endpoint than prostate cancer specific mortality. Because of death benefits claimed by families of veterans, ascertainment of all-cause mortality can be accomplished with 100% completeness. The National Death Index will ensure similar mortality data for nonveteran participants. 2) In the final evaluation, performing a radical prostatectomy is based on the belief that surgical extirpation of prostate cancer will not only free the patient of his cancer but also will prolong his life. Therefore, the ultimate goal of radical prostatectomy is to prolong life in individuals with CAP who are judged to be acceptable surgical candidates. If prostatectomy does not improve all-cause mortality, it is unlikely to be beneficial. Such rationale is supported by the fact that radical prostatectomy is not generally recommended for individuals who are likely to die from nonprostate cancer causes.



Our sample size is sufficiently large to be able to determine with a power of 90% whether radical prostatectomy results in a 15% improvement in overall survival (with an expected median survival of 15 years). This extremely powerful study design and sample size will provide conclusive evidence regarding efficacy of the two treatment strategies. Our study design and size will also be sufficient to determine if radical prostatectomy results in at least a 40% reduction in prostate cancer specific mortality.

## **VII. RATIONALE FOR THERAPEUTIC OPTIONS**

The primary purpose of the study is to compare the overall approach of immediate surgical intervention and follow-up therapy for disease recurrence or persistence to expectant management. The primary purpose is not to test the effect of a particular drug or intervention. Therefore, the types and indications for interventions were specifically written to allow maximum flexibility while still adhering to the primary study purpose.

We chose radical prostatectomy as the initial intervention option because it is the most common therapeutic strategy recommended for patients with clinically localized CAP. Radical prostatectomy as a primary treatment modality for prostate cancer has increased by almost 100% from 1984-1990 and can be expected to rise further as CAP is diagnosed earlier (35). Radiation therapy was not included as a treatment option because of sample size, cost, feasibility and data suggesting that radiation is not superior to prostatectomy (25-28).

The types and indications for interventions were designed to allow maximum flexibility in the radical prostatectomy arm consistent with current clinical practice. Therefore, we have allowed physician discretion in choosing the intervention and indication for postprostatectomy therapy. Patient outcomes will allow us to conclude if the general therapeutic approach of early detection with "aggressive" initial and follow-up intervention for disease persistence or recurrence is superior to expectant palliative management for symptomatic disease progression or evidence of metastatic spread.

The expectant management strategy utilizes specific predefined criteria to characterize symptomatic or metastatic progression. Therapeutic options in the expectant management strategy allow individual physician decision making while adhering to the principal of palliative therapies for

symptomatic progression utilizing the least morbid and costly approaches. Prostatectomy will be allowed in the expectant management group for palliative relief due to predefined symptomatic local disease progression. Physicians and patients will be blinded to PSA results to minimize treatment crossovers or interventions for nonsymptomatic disease progression.

Recent evidence suggests that treatment with total androgen blockade for metastatic prostate cancer prolongs survival (39, 40). Therefore, participants found to develop metastatic prostate cancer will be eligible for total androgen blockade therapy regardless of treatment arm. Participants randomized to prostatectomy will be included in the surgical arm even if prostatectomy is not performed because of positive lymph nodes or intercurrent events. Furthermore, many centers perform radical prostatectomy even in individuals with positive lymph nodes. Such a decision will be left to the discretion of the individual investigators and recorded. Finally, methods described above have been incorporated to minimize early prostatectomy in the expectant management group. If prostatectomy occurs for nonpalliative reasons these individuals will still be included in the expectant management analysis and classified as a protocol violation. Analysis by this "intention to treat" method is consistent with current clinical practice where patients undergo surgical exploration to determine if immediate intervention is indicated.

## **VIII. SECONDARY OBJECTIVES AND ENDPOINTS**

The primary hypothesis of this study is that all-cause mortality is similar in the two treatment strategies: radical prostatectomy and expectant management. Other objectives of this study include:

1. Effect on prostate cancer specific mortality. An adjudication committee, blinded to the treatment arm will assign a cause of death as being definitely, probably or not due to prostate cancer. The analysis will then investigate prostate cancer specific survival.
2. Effect on health status: The SWOG Prostate cancer specific quality-of-life scale, the AUA symptom and bothersome scale, and the SF-36 General Health Status questionnaire will be utilized to determine which of the two treatment approaches provide superior quality of life (41, 42).

3. Effect on disease recurrence: Patients in the prostatectomy arm will be monitored for evidence of disease recurrence by clinical examination, radiologic and laboratory testing. This will assess the efficacy of the initial intervention for complete tumor removal and prevention of disease recurrence.

4. Progression-free survival: The percent of patients who do not have evidence of prostate cancer progression as measured by clinical examination, radiologic and laboratory studies will be recorded. Local, regional and metastatic disease progression will be recorded. Severity of disease progression will be measured by functional status and health status instruments.

5. During the course of a 15-year study, it is likely that interest will emerge in additional laboratory studies not already included. Therefore, serum and tissue samples will be saved and frozen for serologic and pathologic determinants of CAP progression and mortality.

6. Determinants of prostate cancer progression and mortality: The subgroups of particular interest are defined by the following:

- a. Race
- b. Age
- c. Tumor stage
- d. Tumor grade
- e. Tumor volume
- f. Family history of CAP
- g. PSA level and rate of change in PSA
- h. PAP level and rate of change in PSA

7. Use of the Charlson comorbidity index to predict all-cause and prostate cancer specific mortality (43).

## **IX. STUDY DESIGN**

We will conduct a randomized controlled clinical trial comparing two management strategies for clinically localized CAP: 1) radical prostatectomy and early intervention for cancer persistence or recurrence versus and 2) expectant management with palliative therapy reserved for symptomatic or metastatic disease progression.

## **X. PATIENT SELECTION CRITERIA**

### **A. Inclusion Criteria:**

To be eligible for the trial, subjects must meet the following criteria:

1. Age 75 years or younger
2. Clinically localized (T1a, b, c-T2a, b, c, NX, MO) adenocarcinoma of the prostate
3. Diagnosis of prostate cancer within the previous 6 months

### **B. Exclusion Criteria:**

1. Significant coexisting medical conditions that are acute, debilitating or expected to result in a life expectancy less than 10 years or place the patient at unacceptable surgical risk (e.g. evidence of nondermatologic malignancy within the past five years, severe pulmonary, cardiac, renal, or hepatic impairment, myocardial infarction within six months, unstable angina, dementia, or other debilitating illness).

2. Prior surgical (except TURP), irradiation, hormonal or chemotherapy for CAP.

3. Laboratory abnormalities that in the opinion of the Participating Investigator are expected to result in a life expectancy less than 10 years.

4. Evidence of clinically nonlocalized prostate cancer
  - a) PSA > 100
  - b) Bone scan consistent with metastatic disease

c) Other imaging or laboratory studies performed at the discretion of the Participating Investigator indicating that prostate cancer is nonlocalized.

5. Current use of any of the following medications: estrogens, 5' alpha-reductase inhibitors, antiandrogen drugs.

6. Inability or unwillingness to give informed consent.

7. Reasonable likelihood that the patient cannot be followed during the study period.

8. Participation in another intervention research study.

## **XI. PATIENT RECRUITMENT**

Recruitment of participants will be through veterans organizations, and Medicine, Urology, Oncology and Prostate Cancer Screening clinics. Community based efforts will include radio, television and newspaper advertisement. Participating Investigators and clinic coordinators will develop outreach programs with community internists, urologists, oncologists and Prostate Cancer Support Groups. The patient and family educational videotapes will be provided to these individuals and groups to enhance knowledge of the study and provide education about prostate cancer.

Under the direction of the Participating Investigator, each center will review the urologic logs, operating room lists, pathology and laboratory records and cancer registry to identify all patients with CAP who may be eligible for randomization. All eligible patients will be offered randomization and encouraged to view an informational videotape developed for the study. Participating sites will complete and report to the coordinating center a prescreening prostate cancer log with a list of all patients with prostate cancer. Information on this list will include: (a) subjects eligible and randomized; (b) subjects eligible but not randomized; (c) subjects with clinically localized CAP but who are ineligible because of comorbidities. A list of the initial intervention provided to nonrandomized subjects (prostatectomy, expectant management, hormonal therapy or radiation) will be maintained. A previous surgical trial has utilized this method to ensure adequate enrollment and representativeness of participants (44).

## **XII. PATIENT DIAGNOSIS**

Study eligibility will require a pathologic diagnosis of prostate cancer. This will be based on a histologic diagnosis of CAP from core needle or TURP biopsy specimens. Prior to randomization, specimens will be interpreted by the participating centers' local pathology laboratory and the presence of CAP confirmed. For standardization purposes a centralized reading of slides from biopsy (and prostatectomy) specimens will subsequently be performed by Dr. Thomas Wheeler at Baylor College of Medicine in Houston, Texas. To facilitate patient enrollment, central reading will not be required prior to patient randomization. The central pathology report will provide the final histologic grading and pathologic staging. The Gleason grading system will be utilized.

### **A. Staging of CAP**

The TNM staging system will be utilized (45). Both clinical and pathologic staging will be recorded. Eligibility will be based on clinical staging indicating clinically localized CAP. Patients must be prepared to undergo prostatectomy within 6 weeks after registration. Patients will be clinically staged by rectal examination, PSA and bone scan. Patients with evidence of extra-prostatic disease will be excluded. An elevated prostatic specific antigen level (PSA) will not exclude the patient unless the level is markedly elevated ( $\geq 100$  mg/dl). Use of imaging methods such as transrectal ultrasound, CT or MRI scans will be at the discretion of the individual centers. These will not be required for enrollment into this study but the use of such methods will be recorded. Surgical prostate specimens will be sent en bloc to the central pathology laboratory for review and confirmation.

### **B. Clinical Staging System:**

T1: Clinically inapparent tumor, not palpable nor visible by imaging

T1a:  $\leq 5\%$  of TURP specimen and Gleason score  $\leq 7$

T1b:  $> 5\%$  of TURP or Gleason score  $> 7$

T1c: Identified by systematic biopsy performed e.g. because of an elevated PSA

T2: Palpable or visible tumor confined within the prostate

T2a: Palpable nodule (or visible lesion if TRUS performed)  $\leq 1/2$  lobe and confined to the prostate

- T2b: Tumor involves more than half of a lobe but not both lobes, confined
- T2c: Tumor involves both lobes

### **XIII. SCREENING PROTOCOL (Figure 4)**

#### **A. Prescreening Phase**

Potential subjects (men aged  $\leq 75$ ) will be identified through various sources:

- a) Urology, Medical, Oncology, Prostate Cancer Screening clinics
- b) Community Prostate Cancer Support Groups
- c) Pathology and urology logbooks of all prostate biopsies or specimens
- d) Laboratory lists of PSA and PAP values
- e) Referrals obtained from community physicians or media advertisement

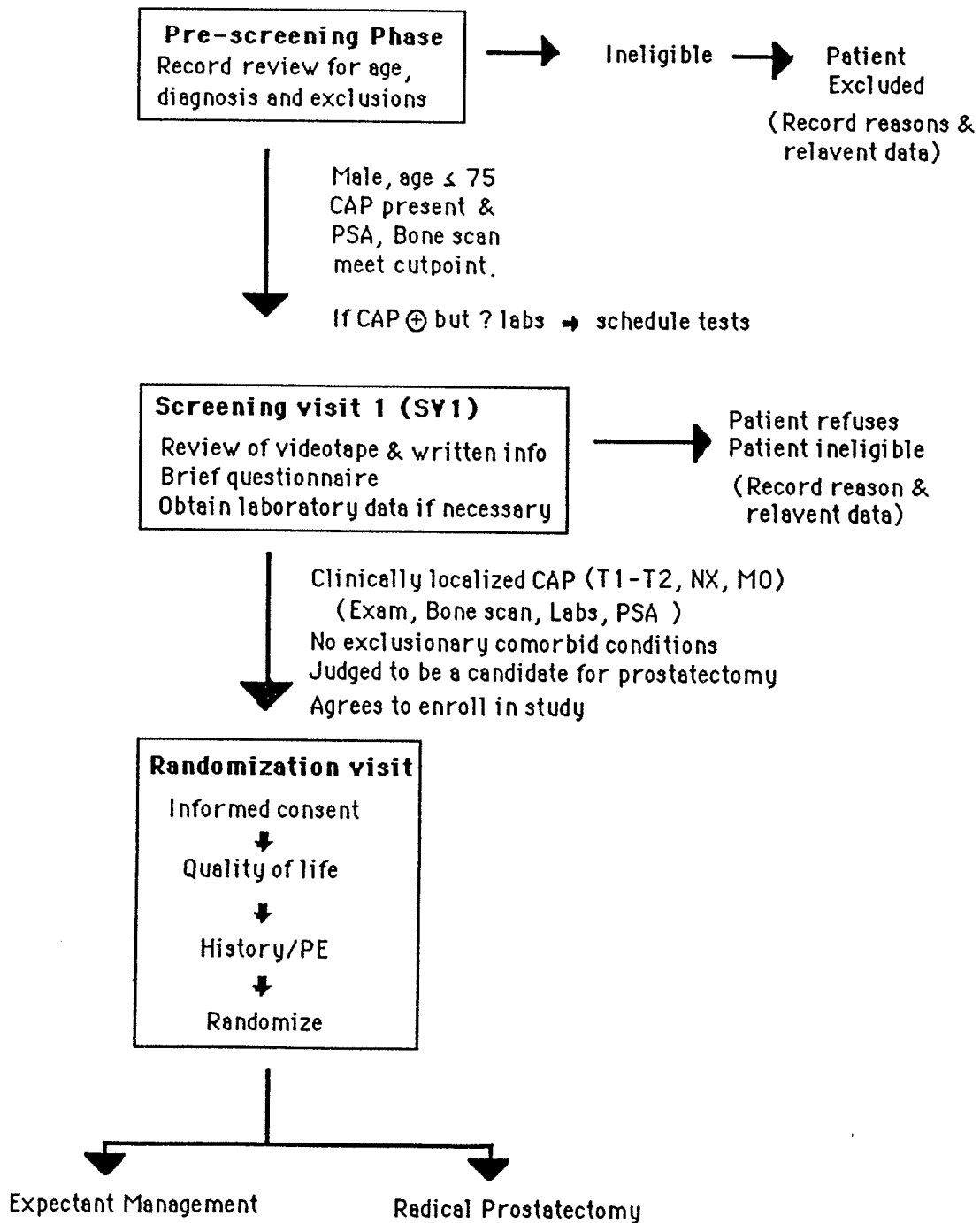
The records of potential subjects will be reviewed and all patients with a confirmed or suspected diagnosis of prostate cancer will be identified. Potentially eligible subjects will be invited to an initial screening visit. All patients with a new diagnosis of prostate cancer will be recorded on the screening log.

#### **B. Screening Phase**

The study will be explained to the individual and family members. They will be encouraged to review the educational study videotape and written materials on prostate cancer. After review of this information, the patient will discuss therapeutic options with the Participating Investigator. If necessary, the patient will be scheduled for laboratory and radiologic tests to confirm the diagnosis of prostate cancer and evaluate the extent of his disease. Patients declining study enrollment will have treatment offered by their primary physician. Screening data will be collected on all patients with prostate cancer: (a) study ineligible; reason for ineligibility recorded, (b) study eligible but refused; reason for refusal recorded, (c) study eligible and enrolled. This will include: age, gender, tumor stage and grade.

Figure 4

### SCREENING PROTOCOL





C. Baseline Visit

Eligible, consenting subjects will return for the baseline visit at which time the following will be performed:

1. History and quality-of-life questionnaires
2. Physical examination including DRE, weight and height.
3. Laboratory studies at the discretion of the PI for evaluation of CAP.
4. The Charlson Comorbidity index to characterize comorbid conditions.

**XIV. INFORMED CONSENT PROCEDURES**

At the second screening visit, informed consent will be sought from eligible subjects by the Participating Investigator. The subject may choose to either read the description of the study or have it read to him. He will be given an opportunity to ask questions, consult with others, and/or have time to "think it over." If the patient consents he will sign, in the presence of a witness, VA Form 10-1086 which contains the information about CSP #407. Form 10-1086 will be placed in the patient's hospital chart with copies to the patient, the patient's study file, the Study Co-Chairman and the coordinating center.

Prior to randomization all subjects will watch the patient introductory information videotape that discusses CAP, treatment options, risks and benefits. This videotape also provides information about the study. The Participating Investigator will be available to answer questions that the patient and/or his family may have regarding the written informed consent, the information videotape and the study.

**XV. TREATMENT REGIMEN AND RANDOMIZATION (Figure 5)**

Patients will be randomized to radical prostatectomy or expectant management. Patients will be stratified by medical center. Baseline data will include clinical stage and grade of the biopsy specimen, PAP and PSA level, age, race, presence of prostatic symptoms, health status, demographics, history of other medical conditions, Charlson Comorbidity index, and family history of CAP.

#### A. Radical Prostatectomy

Patients assigned to radical prostatectomy will receive surgery within six weeks of randomization. In general, this will consist of a lymph node dissection followed by a radical prostatectomy if the lymph nodes are negative for cancer. However, because of variation in surgical practice patterns, some centers may elect to perform a prostatectomy without a prior lymph node dissection. Alternatively, some surgeons perform a radical prostatectomy even in patients with lymph nodes positive for prostate cancer. These different therapeutic approaches will be recorded and analyzed via an "intention to treat" methods of analysis. The surgical procedure (retropubic versus perineal, nerve sparing versus nonnerve sparing) will be at the discretion of the urologist but will be recorded for analysis.

CAP in the prostatectomy group will be classified by pathologic stage as: a) organ confined; b) specimen confined-i.e. capsular penetration with negative surgical margins, seminal vesicles, and lymph nodes; or c) not confined-i.e., capsular penetration with positive margins and/or tumor involving the seminal vesicles and/or pelvic lymph nodes.

#### B. Expectant Management

Participants assigned to expectant management will have therapy reserved for symptomatic or metastatic disease. Treatment for asymptomatic disease progression (e.g. enlarging mass on digital rectal examination or imaging study, or increase in PSA) will not be allowed unless there is evidence of metastasis. Specific criteria defining symptomatic, asymptomatic local, regional and metastatic disease progression are listed in the following section (Patient Follow-up and Interventions). As outlined in the Treatment Decision Tree diagram (Figure 5) interventions are intended to be aimed at relieving patient symptoms.

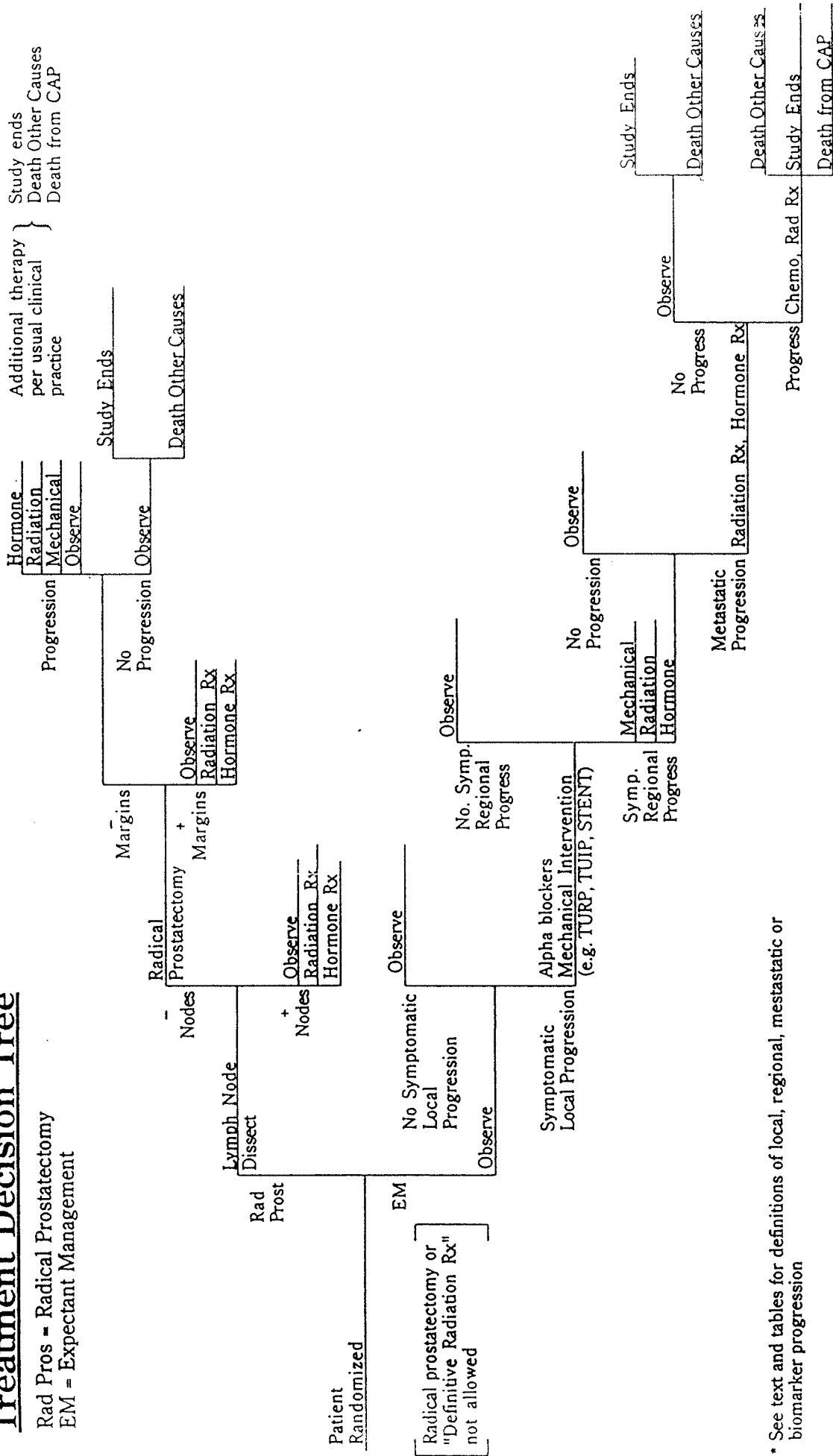
### **XVI. PATIENT FOLLOW-UP AND INTERVENTIONS**

Follow-up examinations for both treatment groups will be identical except that the initial follow-up appointment will be at 6 weeks following randomization in the Expectant Management Group and 1 month postsurgery for the Prostatectomy Group (Table 3). Subsequent follow-up will be every

Figure 5

# Treatment Decision Tree

Rad Pros = Radical Prostatectomy  
EM = Expectant Management



\* See text and tables for definitions of local, regional, metastatic or biomarker progression

3 months for the first year and then every 6 months. Included in this follow-up will be a DRE. Bone scans will be performed annually. Blood for PSA and PAP measurements will be obtained at each visit and evaluated by a central laboratory.

A. Radical Prostatectomy

Participants in the radical prostatectomy group will be allowed follow-up therapy for prostate cancer persistence, recurrence, or progression at the discretion of the local Participating Investigator. The type, timing and reason for intervention will be recorded for subsequent analysis but will not be mandated.

B. Expectant Management

Intervention for participants in the expectant management group must be prompted by evidence of symptomatic or metastatic progression of prostate cancer (Figure 5). To limit the number of interventions being performed for asymptomatic tumor progression, both participants and physicians will be blinded to PSA measurements. PSA and PAP assays will be performed in a central laboratory. In the expectant management group, investigators will be notified of PSA and PAP results that may indicate metastatic disease and prompt further evaluation: i.e. a rise in PSA  $\geq$  100 ng/ml and twice baseline or PAP levels twice normal. Elevations of PSA and/or PAP in the absence of other evidence of metastatic disease will not be an indication for therapy in the expectant management group. The presence of a newly detectable PSA level in participants in the prostatectomy group will also prompt notification to the study investigator.

TABLE 3  
STUDY EVALUATIONS

PARAMETERS	FREQUENCY
CAP DIAGNOSIS	PRESCREENING LOG: CHART REVIEW/BIOPSY/REFERRAL
<u>ELIGIBILITY</u>  PI INTERVIEW/DISCUSSION VIDEO CONFIRMATION TESTING: PSA, BONE SCAN	SCREENING VISIT
<u>ENROLLMENT</u>  INFORMED CONSENT HISTORY/PHYSICAL CLINICAL STAGING QUALITY-OF-LIFE/HEALTH STATUS QUESTIONNAIRE	AT RANDOMIZATION
<u>FOLLOW-UP</u>  HISTOPATHOLOGIC GRADING <u>CLINIC VISITS</u> CLINICAL STAGING PSA, PAP (CENTRAL LAB) QUALITY-OF-LIFE/HEALTH STATUS QUESTIONNAIRE HISTORY/PHYSICAL BONE SCAN TREATMENT FOR CAP DEATH REPORT	POSTOP (SURGERY GROUP ONLY) 6 WEEKS, 3,6,9,12 MONTHS, THEN EVERY 6 MONTHS  ANNUALLY AS PROVIDED WHEN IT OCCURS

In the expectant management group, interventions will be directed at providing palliative relief of the patients presenting symptoms. Initial management considerations will utilize procedures with the lowest morbidity. Patients will not be treated for asymptomatic disease progression/recurrence or evidence of asymptomatic increases in PSA or PAP unless there is evidence of metastasis. Hormonal therapy will be the first line treatment for patients with disease progression requiring nonmechanical therapy. Patients who continue to progress or do not respond to hormonal therapy will be treated with radiation or chemotherapy. Prostatectomy is an option for participants in the expectant management group that have symptomatic local disease progression (defined as recurrent and persistent gross hematuria or bladder outlet obstruction) despite recurrent use of TURP, stents and alpha blockers. The operations manual will clearly specify the criteria required for radiation or prostatectomy in the expectant management group. The Chairman's office will review all prostatectomy or radiation procedures performed and notify centers violating protocol.

Disease progression is defined as follows:

a) Asymptomatic local disease progression/persistence:

- i. New or enlarging mass on DRE, TRUS or other imaging modality
- ii. Persistent tumor despite prostatectomy

b) Symptomatic local disease progression:

- i. Hematuria secondary to prostate cancer progression
- ii. Bladder outlet obstruction due to prostate cancer progression
- iii. A change in the AUA symptom bothersome score due to prostate cancer of 3 points or indicating moderate-severe symptoms ("a lot" or "unhappy")
- iv. Rise in laboratory tests determined to be consistent with prostate cancer: e.g., rise in creatinine, AST, bilirubin to 2X baseline

c) Symptomatic regional disease progression:

- i. Pelvic pain secondary to prostate cancer
- ii. Lymphedema secondary to prostate cancer

d) Asymptomatic regional disease progression:

- i. Hydronephrosis on imaging study with evaluation prompted by creatinine elevation to twice baseline or other evidence of regional progression

e) Asymptomatic metastatic disease progression:

- i. Changes in laboratory tests due to prostate cancer including Hgb < 10.0; abnormal AST, PAP, Bilirubin.
- ii. Abnormal bone scan consistent with prostate cancer
- iii. Radiologic evidence of metastatic disease including bone or chest roentgenograms or abdominal.

f) Symptomatic metastatic disease progression:

- i. Nonpelvic bone pain secondary to prostate cancer

- ii. Decrease in functional status category due to prostate cancer

g) Asymptomatic progression of tumor biomarkers

- i. Increasing or persistent PSA
- ii. Abnormal Prostatic Acid Phosphatase

C. Health Status Surveys

The Prostate Cancer Specific and Overall Quality-of-Life questionnaires developed by Moinpour and administered in previous prostate cancer studies will be utilized (41). They have been demonstrated to have face validity and reproducibility. These surveys will be self-administered prior to randomization and every 6 months. The Prostate Cancer Quality-of-Life and Health Status questionnaire developed by Wennberg and Barry will be utilized to further assess prostate cancer and therapy related symptoms. The AUA prostate symptom and bothersome index will be utilized to assess for prostate specific symptoms (42). The SF-36 health status survey will be employed to assess overall health status including a global assessment of functional status (Table 3).

**XVII. ADHERENCE TO ASSIGNED REGIMEN INCLUDING USE OF VIDEOTAPES**

Centers will be selected, in part, on their willingness to offer randomization to patients fulfilling study criteria. Participating Investigators and Study Coordinators will attend introductory and annual meetings to receive education and review of the study protocol, recruitment, and adherence. In particular, investigators and coordinators will be provided information on patient and family counselling for asymptomatic disease progression.

Patients and family members will be provided educational videotapes and written materials prior to randomization. This information will focus on controversies in the treatment of prostate cancer. Issues related to patient anxiety regarding asymptomatic disease progression in the expectant management group will be addressed. At the annual visit, all participants will review the entry videotape and receive additional written and verbal information about the study and CAP. All centers will be monitored for adherence to study protocol. This will include: (a) number of patients randomized, (b) a log of all patients with prostate cancer, (c) completion of intervention forms to document type of intervention and reason

for intervention in either treatment arm and (d) number of patients violating protocol (e.g. patients in the expectant therapy arm being treated with radical prostatectomy or "curative" radiation therapy). To decrease crossovers in the expectant management strategy, PSA assays will be performed in a central laboratory and only be unblinded and reported if there is a marked rise in PSA levels to  $\geq 100$  ng/mL and twice baseline. Participants will be informed that an increase in a PSA level may indicate disease progression but in the absence of symptoms does not require treatment. All protocol violations will be reviewed by the Co-Chairmen and Data Monitoring Board. Centers will be notified of these violations. Excessive protocol violations will be an indication to terminate centers from the study.

## **XVIII. ENDPOINTS**

All cause mortality is the primary study endpoint because the decision to recommend surgery over expectant therapy for patients with CAP is ultimately based on whether prostatectomy will improve patients overall survival. Death records, Veterans death benefits, the National Death Index and abstraction of medical records will be utilized in ascertaining both all-cause and CAP specific mortality. Secondary endpoints include CAP related mortality defined as mortality due to: 1) widespread CAP, 2) any procedure performed during pre-operative evaluation for radical prostatectomy or other intervention for prostate cancer and 3) occurring within 30 days of surgery for CAP. Assignment of cause of death will be made by the Endpoint Committee blinded to the initial treatment assignment.

Prostate cancer specific morbidity will also be determined. This will include complications resulting from treatment or progression of prostate cancer. CAP morbidity will be classified as: a) local/regional: arising from the prostate tumor; hematuria, pelvic pain, lymph edema, bladder outlet obstruction, b) arising from metastatic prostate cancer; nonpelvic bone pain, weight loss, anemia, etc., c) decrease in functional status as assessed by the previously validated SWOG CAP-Functional Status and Health Status Questionnaire and d) complications from surgery including; incontinence, impotence, colostomy.

Effect on health status will be assessed by the SF-36 General Health Status scale, the AUA prostate symptom and bothersome scale and the prostate cancer specific health status questionnaires. The overall and symptom specific scores during the course of the study on each of these instruments will be compared between the two treatment groups.



Disease recurrence will be routinely assessed by digital rectal examination, PSA and annual bone scans. Evidence of disease recurrence will be classified as symptomatic or asymptomatic and whether there is evidence of local, regional or metastatic prostate cancer. Patients who do not have evidence of disease progression or recurrence by these methods will be classified as having progression-free survival.

A central pathologic laboratory will be utilized for uniform reading of biopsy and prostatectomy specimens. This will provide a central reading of all specimens for baseline characterization of participants and for further analysis regarding prognostic variables (e.g. distribution of Grade and Stage between prostatectomy and expectant management group; predictors of all-cause and prostate cancer specific mortality between the two groups).

A central laboratory will also be utilized to perform PAP and PSA measurements. The following PSA parameters will be utilized for endpoints: a) rate of change in PSA between the two treatment arms, b) percent of participants in the prostatectomy group that have undetectable PSA following surgery, c) percent of participants in prostatectomy group who develop newly detectable PSA, d) percent of participants in expectant management group with PSA > 100 and twice baseline and e) mean baseline PSA in prostatectomy group versus expectant management group. Serum will be stored for future analysis for predictors of disease specific mortality.

Additional baseline data will be utilized to characterize and predict outcomes in participants. This will include race, age, family history of CAP, smoking history and Charlson Comorbidity index.

It is expected that up to 30% of patients with clinically localized CAP will have pathologic evidence of nonlocalized disease at surgery (46). These patients will be included in the surgical group and analyzed via intention to treat methods. Because of the large sample size, it can be expected that randomization will provide equal numbers of pathologically nonlocalized disease in both treatment groups, though it will not be possible to confirm this. We will compare treatment effectiveness in subgroups (including patients with pathologically confirmed localized disease) with the overall study population to define subgroups in whom treatments provide varying efficacy. The decision for surgical intervention is based on clinical not pathologic determination of disease localization. Therefore, we utilized clinical estimates, rather than pathologic determination of disease localization, to determine our sample size.

Our clinical staging criteria are consistent with current medical practice for establishing that a patient is likely to have pathologically localized disease and is therefore a candidate for radical prostatectomy. Our goal was to maximize the likelihood that clinical staging criteria would accurately predict pathologic staging while still reflecting the current medical practice pattern. We will monitor the percent of patients with clinically localized disease found to have pathologically nonconfined cancer. If the percent is found to exceed 30%, the Executive Committee and Data Monitoring Board could recommend that enrollment criteria be altered to improve the correlation of clinical and pathologically localized disease.

## **XIX. STATISTICAL REVIEW**

### **A. Study Design and Outcome Measures**

This study has been designed as a prospective randomized controlled clinical trial to compare two management strategies for clinically localized CAP: radical prostatectomy and early intervention for cancer persistence or recurrence; and, expectant management with palliative therapy reserved for symptomatic or metastatic disease progression.

The primary objective of this study is to evaluate the effectiveness of radical prostatectomy with aggressive management versus expectant management limited to symptomatic treatment in reducing mortality in patients with clinically localized cancer of the prostate. Patients who meet inclusion/exclusion criteria and who sign informed consent will be randomly assigned to one of the treatment approaches. Separate randomization lists will be prepared for each of the participating centers and random assignment will be by telephone to the Perry Point CSPCC. Follow-up clinic visits will be scheduled at 6 weeks, 3, 6, 9 and 12 months after randomization and every 6 months thereafter. It will be necessary to maintain a blind on routine blood tests which will be evaluated centrally. The study will otherwise be unblinded.

The primary outcome measure for this study is death from any cause, i.e., all-cause mortality. In order to further clarify the direct effects of treatment on prostate cancer mortality, each death will then be classified as either death from prostate cancer, death from other cancer or death from other causes. This will be done based on documentation of each death including death certificate, autopsy report, patient chart and other medical records which will be submitted for independent blind review by a study Endpoint

Committee. This committee will have the primary responsibility of correctly classifying each death as CAP related or from other causes.

In addition to the primary outcome, several secondary endpoints related to tumor progression and tumor related symptoms as well as quality of life will be of interest. These will be based on regular follow-up assessments that include: digital rectal exam, urologic symptoms, bone scan, serologic samples for central laboratory evaluation, pathologic/histologic review, PSA testing, and quality-of-life questionnaires. These measures have been discussed in detail above and the detailed plans for analysis are reviewed in the Biostatistical and Research Data Processing (Appendix BRDP) section in Volume II of this proposal.

**B. Sample Size and Study Duration**

The primary outcome measure for this study and the one on which sample size estimates will be based is all-cause mortality. The most current and complete structured literature review of treatment for localized prostate cancer was published coincidentally with the second planning meeting for this study (12). The lead author of that review was a member of the Planning Committee and the estimates and assumptions below are consistent with both the results of that paper as well as other unpublished series reviewed during planning. Based on review of these previous studies, the current best estimate of median survival for patients in the expectant management group is 15 years, i.e., the 15-year survival rate is 50%. In deriving sample size estimates, it is expected that the usual assumptions regarding patient risk (i.e., survival times are exponentially distributed) and patient entry (at a uniform rate during the intake period) that are common to studies involving progressive chronic diseases will also apply in this study. Given these assumptions, the required sample size can be determined by the following method which was developed by Gross and Clark (47) and generalized by Lachin (48,49).

$$SAMPLE\ SIZE = (Z_{\alpha} + Z_{\beta})^2 [F(\mu_e) + F(\mu_c)] + (\mu_e^{-1} - \mu_c^{-1})^2$$

where

$$F(\mu_i) = \mu_i^{-2} \left[ 1 - \frac{\mu_i (\exp[-(T-T_o)/\mu_i] - \exp[-T/\mu_i])}{T_o} \right]^{-1}$$

and where

- $Z_{\alpha}, Z_{\beta} =$  Standardized normal deviate for Type I error rate of  $\alpha$ , and Type II error rate of  $\beta$ .
- $\mu_e, \mu_c =$  mean survival times in the experimental (here, radical prostatectomy) and control (here, expectant management) groups, respectively.

- $T_0$  = time (months) such that patient recruitment begins at time 0 and ends at time  $T_0$ .
- $T$  = time (months) such that  $(T-T_0)$  represents the minimum follow-up of the last patient randomized for the purpose of final analysis. This method assumes patients will enter the trial uniformly over the period  $(0, T_0)$  and all patients will be followed through time  $T$  where  $(T-T_0)$  is referred to as a "continuation period".

This approach offers a number of advantages. It provides a means of incorporating survival times as the basis of sample requirements and relates these to both length of intake and length of a follow-up period beyond the end of intake. While based on mean survival time it can be modified to obtain sample requirements in terms of median survival by noting the constant multiple relationship between the mean and median of the exponential distribution (where Median = Mean \* ln2). Further, estimates can be derived for clinical effects of detectable interest both in terms of either increases in median survival or the corresponding increases in proportion surviving (or conversely, reductions in mortality rates) at the median survival time. This is based on the definition of the hazard rate,  $\lambda$ , in terms of the proportion surviving,  $p$ , given by  $\lambda = -\ln(p)/t$ , for a given time,  $t$ , under the exponential properties of constant and proportional hazards (47). Sample size estimates have been derived for several levels of parameters of interest including percentage increase in median survival (with the corresponding reduction in cumulative mortality rate), length of intake period, length of follow-up after intake ends, and statistical power for two-tailed alpha (Type I error) of 5%, assuming median survival of 15 years. These estimates are presented in Table 4. In general, for fixed levels of detectable clinical effects, decreasing either the intake or follow-up period (or both) has the effect of increasing sample size requirements and increasing study costs. In reviewing such factors as length of study, availability of centers, the expected per center yearly enrollment rates (estimated at 8-12 patients per year), the importance of long-term follow-up for prostate cancer and the costs associated with respective trade offs related to combinations of these factors, the Planning Committee has decided on a 15-year study comprised of a 3-year intake period and a 12-year follow-up period. Further, the power of the study (90%) should be sufficient to detect at a minimum a clinical effect of a reduction in mortality rate of 15% (25% increase in median survival). From Table 4, it can be seen that a recruitment goal of 2000 patients, 1000 on each treatment arm, will satisfy these requirements. This goal is quite conservative in the view of the Planning Committee in that this study is powered to detect relatively small but clinically important clinical effects. The results should be convincing to the medical community one way or the other. That is, a 15-year study of 2000 patients showing no obvious benefits for radical prostatectomy will provide a conclusive answer to the perplexing dilemma for which the study was developed. As an example of the small clinical effects that the study has been designed to detect, simulated survival curves for three samples sizes from Table 4 appear in Figure 6 where they are contrasted with a curve centered at 50% at 15 years.

Table 4

Number of Patients per Treatment Group for Different Levels of Statistical Power, Length of Intake, Length of Follow-up for Type I Error of 5% (2-Tailed) Assuming Median Survival of 15 Years

Percentage Reduction in Mortality Rate		Corresponding Increase in Median Survival Time	Power	Intake (Years)											
				2				3				4			
%	From 50% to	Delta (%)		Follow-up (Years)											
				10	11	12	10	11	12	10	11	12	10	11	12
10	45.0	16	85	2199	2056	1936	2126	1995	1883	2059	1938	1835	2059	1938	1835
15	42.5	25	90	2573	2406	2265	2488	2334	2204	2410	2268	2147	2410	2268	2147
20	40.0	36	85	977	913	859	944	885	836	914	860	814	914	860	814
25	37.5	47	90	1143	1068	1005	1105	1036	978	1070	1007	953	1070	1007	953
			85	552	516	485	533	500	472	516	486	459	516	486	459
			90	646	603	568	624	585	552	604	568	538	604	568	538
			85	355	331	311	343	321	303	332	312	295	332	312	295
			90	415	388	364	401	376	354	388	365	345	388	365	345

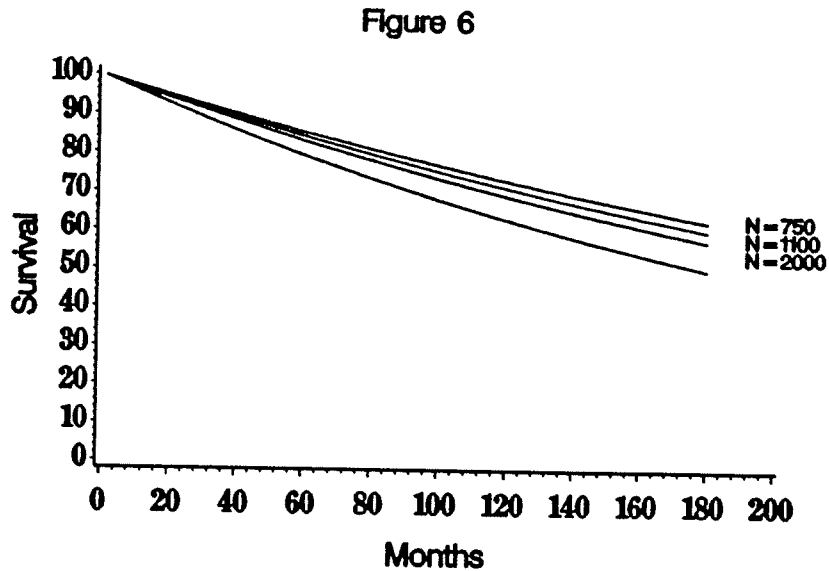


Figure 6: Simulated Survival Curves for Three Select Sample Sizes  
Relative to Survival of 50% at 15 Years

A secondary but important endpoint that will also be evaluated is cancer specific mortality. It has been estimated by the Planning Committee that 15-year cancer specific mortality would be expected to range from 15%-25%. The committee also decided that a convincing study would be one that could detect at least a 50% reduction in cancer specific mortality. The sample size calculations were repeated as above for a number of levels of parameters related to cancer specific mortality. These studies showed that the goal of entering 2000 patients is quite conservative with respect to cancer specific mortality. That is, if the lower estimate of 15% mortality were used (resulting in the highest sample size), the study is sufficiently powered to detect reductions in mortality of at least 40%.

Because of the availability of benefits systems and/or death registries and the advantages they provide in tracking patients, it is expected that the date of death will be determined for all patients. The study will require the enrollment of 667 patients per year during the intake period indicating that, conservatively, 60-80 participating centers will be required. In order to mount a clinical trial of this size, the study has been planned as a joint collaborative trial involving both the VA Cooperative Studies Program and the National Cancer Institute, which through its infrastructure of national and regional oncology groups, ensures the feasibility of completing the study. Within the VA, a great deal of interest has been expressed in participation in this study. At the time of submission, more than 40 VA centers have expressed an intention to participate. These centers are listed in Volume II of this proposal (see Participation).

### C. Statistical Analysis

The primary outcome variable for this study is all-cause mortality, death from any cause. The comparison of the relative effectiveness of the two treatment management approaches, radical prostatectomy and expectant management will be based on a survival analysis of time to death as measured from the time of randomization. Survival curves for each of the treatment groups will be estimated with Kaplan-Meier methodology and treatment group comparisons will be based on the logrank test. The analysis will be conducted on an "intention to treat" basis.

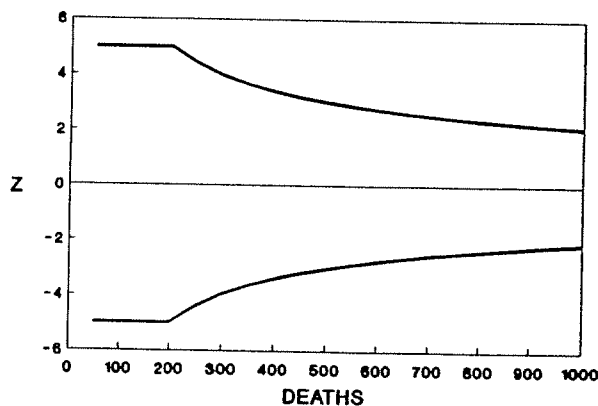
Each death will subsequently be classified with respect to the direct effects of prostate cancer. Treatment groups will then be compared as in the primary analysis outlined above but based on mortality due to prostate cancer. In addition to the primary analysis of mortality, patients will be monitored routinely during follow-up on a number of secondary measures. These are related primarily to tumor recurrence or progression with related symptoms and include physical symptoms, quality of life, and types of treatment that have been provided for CAP symptoms. For a number of these measures, the primary objective of data analysis will be largely descriptive. In the radical prostatectomy arm, recurrence will be of primary interest and summary statistics regarding associated rates and symptoms will be developed. In the expectant management arm, tumors will remain intact and summary statistics will be developed for progression and metastatic rates along with statistical characterization of associated symptomatology. Likewise, since the two treatment arms require essentially different applications of available symptom management procedures, both in timing and amount, the strategy will be to develop statistical summaries of treatment in order to characterize the two study treatment arms. Descriptive statistics for surgical events including types and associated rates of complications will be developed. An important consideration in evaluating the study interventions is the overall quality of life as experienced by study patients. The study measures include a number of standard scales for assessing quality of life and direct comparisons between treatment groups will be performed. The scales are usually ratings and will be compared by analysis of variance procedures. Both individual scales and derived composite scores will be of interest and therefore subject to this analysis. The complete details of the data analysis including presentation formats are provided in the Biostatistical and Research Data Processing (Appendix BRDP) section in Volume II of this proposal.

### D. Interim Monitoring and Repeated Significance Testing

The responsibility for independent monitoring of this proposed study once ongoing will be assumed by the Data Monitoring Board. This committee meets periodically in order to review accumulating

results in order to determine whether the study should continue. The current schedule is to meet at start-up, after nine months, and annually thereafter. When repeated significance tests are performed on accumulating outcome data as part of a "stopping rule" or periodic monitoring function, the overall Type I error rate for the study can change dramatically. This statistical problem has received considerable attention in the literature and the reviewer is referred to general texts (50,51) for a detailed discussion and additional references. Briefly, it can be shown that as the number of repeated tests increases so does the overall Type I error rate. For example, the overall Type I error rates for 5, 10, and 20 repeated tests all at the 5% level of significance are 14%, 19% and 25% respectively (52). Several different methods have been developed for dealing with this problem (50), all of which rely on adjusting the significance levels of the individual tests so that overall protection is maintained at a prespecified level. It will be proposed that as part of this protocol, a monitoring rule be adopted as follows. At each of its annual meetings, the Data Monitoring Board will review the results of the primary analysis. Specifically, the logrank statistic will be computed after every 50 deaths and will be compared to a set of monitoring boundaries derived from methodology proposed by Lan and DeMets (53). This approach produces boundaries such that if the p-value of the logrank statistic exceeds the p-value associated with the boundaries, the committee should recognize that an important "warning" has been signaled. That is, there is reliable evidence of early differences that may be conclusive upon further review and in fact, lead to a recommendation for early termination. The Lan-DeMets procedure produces decision boundaries that are quite conservative over the first several "looks" and which gradually converge to the nominal alpha levels as the final "look" is approached. Figure 7 provides as an example a graphical presentation of Lan-DeMets boundaries for 20 "looks".

FIGURE 7





## **XX. FEASIBILITY AND COLLABORATION WITH THE VA AND NCI**

A total of 2000 patients will need to be enrolled in this study. Estimates from the Patterns of Care Study indicate that approximately 30,000 radical prostatectomies are performed annually. Current data indicate that 66% of patients with Stage A and 17% of Stage B prostate cancer have expectant management for their prostate cancer.

We anticipate the number of patients eligible for prostatectomy to increase as the frequency of screening for CAP increases. In fiscal year 1992, the patient treatment file (PTF) indicated that 1,530 radical prostatectomies were performed at VAMC's. This represents a 12% increase from 1991. Our discussion with participating medical centers indicate that the PTF underestimates by as much as 5-fold the number of prostatectomies performed. Additionally, these data do not include information about subjects with clinically localized CAP who received radiation or expectant management as initial therapy who may be eligible for this study. Therefore, the number of patients from VAMC's who will be eligible for this study will be greater than those having received prostatectomy.

Based on previous surgical case records, an active screening program will not be necessary at VAMC's to detect sufficient number of cases of clinically localized CAP for this study. We estimate that participating VAMC's will be able to enroll an average of 10 patients/VAMC/year or 30 patients/VAMC/study. This results in less than one patient per month assigned to prostatectomy and should be feasible at VAMC's. This would result in 1,350 patients enrolled from 45 VAMC's. Centers concerned that participation will reduce the number of prostatectomies available for resident training can be reassured that on average only five patients/year who are candidates for prostatectomy would not receive this operation.

The National Cancer Institute, through the Southwest and Eastern Oncology Groups (SWOG and ECOG) Cancer And Leukemia Group B (CALG-B), has a large network of medical centers (both university and community based) that have successfully recruited for many clinical trials. We have received a formal commitment for participation and support from Dr. Richard Kaplan of the National Cancer Institute and the Prostate Organ Chairmen of SWOG, ECOG and CALG-B (See letter and Appendix). Using 35 SWOG/ECOG sites would require enrolling 6.2 patients/NCI center/year at NCI sites (18.6 patients/NCI center/study). Many VA investigators have SWOG/ECOG/CALG-B affiliation. This will facilitate patient enrollment and ease operational complexity.

If recruitment is slower than anticipated a fourth year of enrollment could be added without additional expenses because of our use of a capitation system. This would result in a mean follow-up of 13 years (rather than 13.5 years) and will have little effect on study power (See Table 4 in Sample Size Section). If a fourth year of enrollment was necessary, centers would then have to enroll at a rate of 7.5/year at VAMC's and 4.6 patients/year at NCI sites.

## **XXI. VA AND NCI COLLABORATION AND FUNDING OF CENTERS**

This proposal is a joint collaboration between the Department of Veterans Affairs Cooperative Studies Program and The National Cancer Institute. Representatives from both the VA and NCI have served on the planning committee and have approved the proposal, the collaborative agreement and the funding mechanisms outlined below.

We have proposed a capitation system as the most feasible method for reimbursement. All participating centers have past experience in conducting clinical studies using similar reimbursement methods. They have data managers in place that can assist with data collection. Data collection forms have been simplified to collect only essential information for the main outcome measures.

We will reimburse centers for efforts related to patient recruitment, enrollment and follow-up. This will include funding for completion of a monthly Participant Prescreening Log, eligible participants viewing the informational introductory videotape, randomized participants, follow-up visits and the costs for processing and shipping of samples specifically required for this study. The exact method of reimbursement will be outlined in greater detail in the budget justification section.

We have reviewed other funding options such as full- or part-time data managers at each center. Because of the large number of centers required for this study, the relatively few patients enrolled per center and the limited additional follow-up required for study evaluation beyond usual clinical practice, we do not believe that a dedicated data manager could be justified.

This should be feasible given the expected total enrollment of 10-50 patients/per center and scheduled biannual visits. We anticipate that unscheduled visits will result in an average of 4 visits per year.

The patient population served by the VA is representative of those who would most benefit from and in whom this study is most feasible. The Death Records maintained by the VA will ensure essentially

100% follow-up for mortality statistics. Patients followed in the VAMC's will be less likely than patients in private care to receive treatment out of protocol.

The VA has a long history of conducting cooperative surgical trials. Randomization of participants to surgery versus expectant management is not unique to this study. Recent information in the medical and lay press have heightened physician and patient interest in the controversies surrounding treatment of clinically localized prostate cancer. This should assist with participation in our study. This is supported by the fact that so far 47 VAMC's as well as the NCI oncology groups have already agreed to participate.

All procedures, tests and analyses are feasible within the VA and the VA Cooperative Studies Program. The VA Cooperative Studies Program has previously instituted a cooperative study of surgery versus observation for early CAP (VACURG 2). However, this study was of inadequate size to definitively answer the primary study question. Other urologic and surgical VA cooperative studies of similar or greater size to our proposal involving surgery versus expectant management have been conducted. These include subjects with asymptomatic as well as symptomatic disease.

Videotapes and interactive videodiscs have been developed and will be modified to assist with patient education and recruitment for this study. Recruitment of participants will be through veterans organizations, medical and urologic clinics, prostate cancer support groups, NCI newsletters, television, radio and newspaper advertising. The clinical coordinator and Participating Investigator from each center will review the urologic logs, operating room lists, pathology records and cancer registry to identify all patients with CAP who may be eligible for randomization. All eligible patients will be offered randomization. The coordinators will report to the coordinating center a list of four groups: (a) those eligible and randomized; (b) those eligible but not randomized; (c) those eligible but with medical exclusions for which our protocol proscribes entry into the trial and (d) those who do not fulfill our baseline criteria but undergo prostatectomy. A previous surgical trial has utilized this method to ensure adequate enrollment and representativeness of patients (44).

## **XXII. MONITORING THE STUDY**

The groups charged with monitoring the various aspects of the study will be: the Executive Committee, the Data Monitoring Board, the Human Rights Committee, and the Endpoint Committee. These committees will meet at regular intervals according to the prevailing practice of the Cooperative Studies Program.

A. Executive Committee

This committee will consist of the Study Co-Chairmen, the Study Biostatistician, 3-4 Participating Investigators, the director of the central pathology laboratory, and NCI representatives. It is the management and decision-making body for the operational aspects of the study. One of its responsibilities is to monitor the performance of the participating medical centers.

B. Data Monitoring Board

Sixteen members will be nominated including specialists in prostate cancer and four biostatisticians. From these nominations, eight including two statisticians, will be selected to form the DMB. They will review the progress of the study and monitor patient intake, outcomes, and ethical issues. The Board will make recommendations to the Chief of the Cooperative Studies Program and the National Cancer Institute whether the study should continue or be terminated. We suggest that the Data Monitoring Board should consider the following circumstances as grounds for early termination: 1) compelling internal or external evidence of treatment differences, and 2) infeasibility of addressing the study hypothesis (poor adherence, low event rates, poor patient intake). Interim analyses will be provided to the DMB by the Study Biostatistician.

C. Human Rights Committee

This committee will meet every 12 months in conjunction with the Data Monitoring Board to ensure that the patients' rights and safety are being properly protected. In the interim, they may be asked to convene if there is any serious event requiring their attention. They will be presented with a report from the Study Biostatistician as to the progress of the study and ethical issues relevant to the Human Rights Committee.

D. Endpoint Committee

This committee will consist of three independent urologists or experts in prostate cancer and one of the Study Co-Chairmen as a non-voting member. Prior to the start of the study, this committee will establish diagnostic criteria and procedures for endpoint determination. They will review all deaths to make a final determination as to whether or not it was cancer related.

E. Participants-Study Group

Forty-five VA Medical Centers and thirty-five National Cancer Institute centers will be selected to participate. The study group will consist of the Participating Investigators and permanent consultants. They will meet to discuss the progress of the study and any problems encountered during the conduct of the trial. Though this study will not be blinded, overall summaries of study outcomes will not be presented to this group.

F. Monitoring Patient Intake

The intake and operational aspects of this study will be monitored continuously by the Study Co-Chairmen and Study Biostatistician. Participating medical centers will continue in the study only if adequate patient intake is maintained. These actions will only be taken with the concurrence of the Data Monitoring Board or by administrative action of the Central Office.

If recruitment is not proceeding at an appropriate pace, reasons for patient exclusion will be scrutinized by the Co-Chairmen and the Study Biostatistician. Based on this information the Executive Committee may choose, with the approval of the Data Monitoring Board and Cooperative Studies Evaluation Committee, to extend the recruitment period in some or all centers, to add additional centers, or to make minor modifications to the entrance criteria.

G. Monitoring Medical Center Performance

Strict adherence to the protocol will be expected of every participating center and monitored by the Data Monitoring Board, the Executive Committee and the Study Group. A log of all patients with prostate cancer, their reasons for exclusion and inclusion will be collected by the participating centers and reviewed by these committees. Documentation of protocol breaches will be required and the medical centers with repeated protocol violations will be recommended for termination to the Data Monitoring Board. If a Participating Investigator feels that adherence to the protocol will in any way be detrimental to a particular subject's health or well-being, the interest of the patient must take precedence.

By agreeing to participate in the study, the medical center delegates responsibility for global monitoring of the ongoing study to the Cooperative Studies Program committees and personnel listed above. However, the Research and Development and the Human Studies Subcommittees of the medical center

may require Participating Investigator to submit annual and final progress reports concerning the status of the study at the medical center for local monitoring purposes.

### **XXIII. PUBLICATION POLICY**

All publication policies will be decided by the Executive Committee.

The primary publication (s) directly related to the objectives of this Cooperative Study Protocol will be authored by the Study Co-Chairmen, the Study Biostatistician, and, as deemed appropriate by the Executive Committee, other Participating Investigators who have made significant contributions to the writing of the manuscripts. All study participants will be included on the author line as "and the CS407 Study Group."

Acknowledgment must be given on all publications to all participants, members of the Executive Committee, Data Monitoring Board, consultants, supporting personnel of the CSPCC, and the Central Administration of CSP. The statement, "Supported by Cooperative Studies Program Medical Research Service, Department of Veterans Affairs Central Office, Washington, D.C. and the National Cancer Institute, Washington, D.C." must be included in all publications.

Authorship of secondary publications related to the protocol will be decided by the Executive Committee. Data derived from the cooperative study are the property of the Cooperative Study Group, not the property of the individual Participating Investigator or the health care facility where the data were generated. By participating in the cooperative study, participants agree to accept the principle that results from their individual health care facility will be published separately only with the approval of the Executive Committee.

Any publication related to the major endpoints or outcomes during the active phase of the study must have the prior approval of the Data Monitoring Board. All manuscripts are to be approved by the Chief at the Coordinating Center before submission for publication.

### **XXIV. QUALIFICATIONS OF PARTICIPATING CENTERS**

1. There will be a Participating Investigator (PI) at each center. PIs who are not themselves urologists must identify a collaborating urologist at their institution.

2. The urologic surgical team at the participating center should have performed at least 10 radical prostatectomy procedures per year for the previous two years with an operative mortality less than 3%.

3. A staff urologic surgeon must be scrubbed on all study procedures.

4. A pathology department must be willing to provide biopsy and surgical specimens for central reading.

## **XXV. HUMAN RIGHTS CONSIDERATION**

The need for a randomized trial has been recognized before, but always with the caveat that the study would not be ethical because surgery is the generally accepted treatment. The problem with this ethical position is that ineffective or toxic therapies can never be discarded. In a more contemporary formulation, a randomized trial is considered ethical when a state of "clinical equipoise" exists; i.e. when there is sufficient scientific uncertainty to result in honest professional disagreement among expert clinicians, even though any individual may believe one treatment to be clearly superior. The currently available data do not define a superior therapeutic strategy and suggest clinical equipoise. Recent analyses of available data for different therapies in localized prostate cancer have been unable to provide definitive statements on the preferred therapy. They have concluded that a clinical trial comparing prostatectomy versus expectant management is not only ethical but necessary to determine whether prostatectomy improves survival and quality of life in patients with clinically localized prostate cancer compared to expectant management with palliative treatment reserved for symptomatic disease progression.

Theoretically, radical prostatectomy can provide curative therapy for localized CAP. However, radical prostatectomy has perioperative morbidity and mortality. Combined with CAP persistence, recurrence, CAP and non-CAP deaths in the prostatectomy group, these factors may eliminate the benefits of surgery. Expectant management with palliative treatment for symptomatic or metastatic disease progression may be equally effective in patients with localized CAP and not expose them to the risk of surgery or early and toxic adjuvant therapy. However, these patients may develop symptomatic or metastatic disease progression that perhaps could have been prevented from early prostatectomy. The questions exist: is a potentially curative procedure possible in those whom it is necessary and is it necessary in those for whom it is possible? Only a randomized trial as outlined in our proposal will answer these questions.

## **XXVI. BUDGET JUSTIFICATION**

We have proposed a capitation system as the most feasible method for reimbursement. Participating centers have past experience in conducting clinical studies using similar reimbursement methods. Most have data managers in place that can assist with data collection. Data collection forms have been simplified to collect only essential information for the main outcome measures.

All patients with prostate cancer will be recorded on monthly prescreening logs to enhance enrollment and determine comparative baseline characteristics of enrolled and nonenrolled men with CAP. Eligibility data, identification of patients scheduled to view the introductory informational videotape, and initial treatment of those patients not randomized will also be collected. This will require that data managers or Participating Investigators conduct a regular review of the pathology biopsy report books and a brief chart review. To ensure timely and complete data collection, we will pay each center \$150 per monthly prostate cancer prescreening log completed.

For each eligible subject that has signed a log stating they have viewed the introductory videotape, centers will be reimbursed an additional \$50 up to a maximum of \$5000/center/year. This will assist in motivating centers to encourage potential participants to be made aware of our protocol.

It is anticipated that each center will have reviewed records of at least 100 patients, logbooks, laboratory lists and patient support groups to enroll the goal of 10 patients per year. A reimbursement of \$1000/patient enrolled will be offered as additional incentive for centers to randomize patients. This reimbursement will be necessary to assist in the initial patient evaluation and first year follow-up. This payment can be applied towards the salary of a data manager at the discretion of the local Participating Investigator. Enrollment for this study will take considerable effort to explain the risks and benefits of the different treatment strategies and to answer any questions patients and families may have even after viewing the educational videotape.

The Participating Investigator will be responsible for 5 visits/patient the first year of enrollment and semiannual visits after that. It is also anticipated that many patients will make unscheduled visits for prostate cancer related concerns. Therefore, we will reimburse centers \$400/year/for years 1-4 (\$450 years 5-9 and \$500 years 10-15) for patient follow-up. To assist in applying this reimbursement toward data managers, we will provide 50% of the anticipated annual reimbursement at the beginning of each year. Therefore we anticipate the annual enrollment reimbursement for an average center will be: 12 monthly logs (\$150/log); 75



patients watching the videotape (\$50/patient); 10 patients randomized (\$1000/participant) = \$15,500. To encourage centers to enroll beyond goal (and keep the study ahead of recruitment schedule), we will include an incentive bonus of \$100 per patient for centers enrolling more than 15 patients per year. We have reviewed other funding options such as full- or part-time data managers at each center. Because of the large number of centers required for this study, the relatively few participants enrolled per center and the limited additional follow-up required for study evaluation beyond usual clinical practice, we do not believe that a dedicated data manager could be justified. Each center is provided with \$1200 per year during the recruitment phase to assist with operating costs.

The patient information and educational videotape is critical for participant recruitment. Each center will be provided three copies of the videotapes so that families can "sign them out" and view the videotapes at home if desired. The start-up costs of making the educational videotape are largely covered through other research funds. However, the specifics of our study have been incorporated into this videotape and therefore require that a reimbursement above the cost of the videotape be included.

Because of the large number of centers and participants involved and the collaboration of the VA with the NCI, the following administrative support is needed in the Chairman's office:

Dr. Wilt:                      Project Administrator (GS-11)  
   Project Program Assistant (GS-5)

The Chairman's office will require a FAX machine and two computers for data input, communications, newsletters etc.

All examinations, therapies, and laboratory tests except those mentioned above, are considered within the context of standard clinical practice and, therefore, should be performed at the local centers at no costs to the study.

## **XXVII.            JUSTIFICATION OF CENTRAL LABORATORY**

Funding is requested for processing, shipping and central measurement of prostate specific antigen (PSA). This biomarker is a sensitive measure of disease progression. In an attempt to minimize patient crossover due to an asymptomatic rise in PSA, we are blinding PSA and having this measured in a central location. A central laboratory using standardized assay techniques is also necessary to accurately measure

baseline PSA and change in PSA. The central laboratory will notify local centers if a PSA measurement rises to a predetermined "action level." This laboratory will also serve as a serum bank for additional serologic analyses.

Funds are requested for mailing tissue biopsy and prostatectomy specimens. It is critical that a central standardized reading of the specimens is obtained to ensure reliable description of our study population and assess for predictors of all-cause or prostate cancer specific mortality.

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**APPENDIX A**  
**HUMAN RIGHTS REVIEW**  
**AND**  
**INFORMED CONSENT**



May 27, 1993

Joseph Collins, Ph.D.  
Chief, Cooperative Studies  
Coordinating Center  
V.A. Medical Center  
Perry Point, MD. 21902

Dear Dr. Collins:

The Human Rights Committee (HRC) met with the Planning Committee on Tuesday, May 25, 1993, at the Omni Inner Harbor Hotel, in Baltimore, Maryland to review VA Cooperative Study #407: Prostate Cancer Intervention Versus Observation Trial (PIVOT): A randomized trial comparing radical prostatectomy versus palliative expectant management for the treatment of clinically localized prostate cancer.

The HRC met with Dr. Collins to discuss and review the aforementioned protocol. Later on, at a joint meeting with the Planning Committee, the Principal Proponents, Drs. Timothy J. Wilt, M.D. and Michael K. Brawer, M.D. gave the HRC an overview and an update of the study.

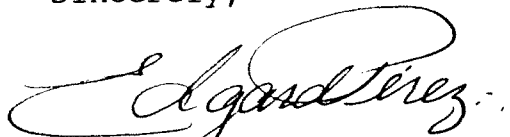
Afterwards, the HRC Committee reconvened making the following recommendations:

- o Principal proponents to do a complete re-write of the inform consent, beefing up areas not clear, including all verbal recommendations given by the HRC, i.e.; Procedures: Clarify the two types of procedures. As presently written, it gives the impression of 6 different procedures, when in fact there are only two. Procedure 2, 3 & 4 should be 1a, 1b, and 1c.. Procedure # 5 should be #2 and Procedure # 6 should # 3.
- o Page 15 of the protocol Sec. VIII. SECONDARY OBJECTIVES AND ENDPOINTS: Rewrite this paragraph deleting "primary hypothesis" and "aggressive" etc.
- o HRC to receive a copy of the script for the training Video, and at a later date to have the opportunity to view the Video.
- o The purpose of the Video is to ensure the standarization of the training of personnel who will be administering the inform consent. Through this process, study participants will have a consistent interpretation of the purpose of the study.



Once the aforementioned revisions have been made the HRC Committee will meet in a separate meeting to discuss and give our determination for this study.

Sincerely,

A handwritten signature in cursive script that reads "Edgard Pérez". The signature is written in black ink and is positioned above the typed name.

Edgard Pérez, Member  
Human Rights Committee, CSP

HRC Attendees

Martin Feldbush  
Susan Leviton  
Maurice Moore  
Thomas Hobbins  
Robin Weiss  
Joe Libonati  
Edgard Pérez

July 20, 1993

Joseph Collins, Ph.D.  
Chief, Cooperative Studies  
Coordinating Center  
V.A. Medical Center  
Perry Point, MD 21902

Dear Dr. Collins:

The Human Rights Committee (HRC) met with the Planning Committee on Friday July 16, 1993, at the Omni Inner Harbor Hotel, in Baltimore, Maryland to review VA Cooperative Study #359: "A Clinical Trial Comparing the Safety and Efficacy of Alpha Blockade and Androgen Suppression for the Treatment of Benign Prostatic Hyperplasia".

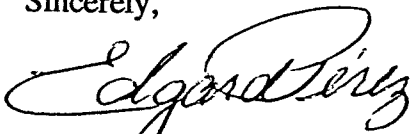
The HRC met with Dr. Collins to discuss and review the aforementioned protocol. Later on, at a joint meeting with the Planning Committee, the Principal Proponent, Dr. Herbert Lepor, MD, gave the HRC an overview and an update of the study.

The randomization of this study is going well, and the use of the drugs has not been problematic.

Additionally we reviewed two revised consent forms for CSP #398 "The Efficacy of Tactile-Thermal Application for Treatment of Dysphagia Resulting from Stroke", and CSP #407 "Prostate Cancer Intervention Versus Observation Trial (PIVOT): A Randomized Trial Comparing Radical Prostatectomy Versus Palliative Expectant Management for the Treatment of Clinically Localized Prostate Cancer".

The revisions of the aforementioned revised consent forms were greatly improved and since the CSP #359 was going well with no human rights issues detrimentally affecting the participants, the Human Rights Committee approved them all.

Sincerely,



Edgard Perez, Member  
Human Rights Committee, CSP

HRC Attenders:

Susan Leviton, Joe Libonati, Maurice Moore, Edgard Perez, and Thomas Hobbins (Via Telephone Conference)



Subject Name: \_\_\_\_\_ Subject # \_\_\_\_\_

Participating Investigator: \_\_\_\_\_ Date: \_\_\_/\_\_\_/\_\_\_  
Mo Day Yr

VAMC Name: \_\_\_\_\_ VAMC # \_\_\_\_\_

Title of Study: Prostate Cancer Intervention Versus Observation Trial (PIVOT):  
A Randomized Trial Comparing Radical Prostatectomy Versus Palliative Expectant  
Management for the Treatment of Clinically Localized Prostate Cancer - CSP #407

**DESCRIPTION OF RESEARCH BY INVESTIGATOR**

**PURPOSE:** You have been asked to take part in this research study because you have cancer that is without sign of spread beyond the prostate. The purpose of this study is to find out whether treatment of prostate cancer by immediate surgery to remove the prostate (called radical prostatectomy) and immediate intervention for any reappearance of cancer is better than closely watching, waiting and treating symptoms if and when cancer progresses (called expectant management). Both treatments being given in this study have been used routinely but are now being studied to compare the benefits and effectiveness of each. The study is planned to last a total of 15 years. The following provides a brief explanation about prostate cancer and options that are available for treatment.

Background information about prostate cancer: Cancer of the prostate (CAP) is the most frequently diagnosed nonskin cancer and the second leading cause of cancer related deaths. CAP increases with age, with the most common age at diagnosis of 72 years. There is a high frequency of cancer in the prostate found at autopsy of men who die of other causes. Because of the slow progression rate of the tumor, the age and other medical conditions at diagnosis, men with CAP are more likely to die from some other cause. Other studies have shown that 30% of men over the age of 50 have prostate cancer and that only 1 in 200 men will die directly from prostate cancer. However, if CAP progresses to be detectable by physical exam, death from CAP increases to one in four.

Expectant management in treatment of prostate cancer: Previous studies show that the chances of being alive after 10 years is about the same whether men receive immediate surgical removal of the prostate or expectant management. Because of this, doctors in Europe and Scandinavia generally recommend expectant management. This treatment, however, does not offer the possibility of cure that might result from removal of the prostate. Treatment by expectant management does avoid any of the serious complications including death that can occur at the time of surgery. It is currently used in between

20%-30% of men with prostate cancer that have no sign of spread outside of the prostate. If symptoms develop, they have generally been successfully treated with hormone therapy, surgical procedures that will maintain normal urine flow or local radiation treatment. That is, symptoms can be treated without removing the prostate by radical prostatectomy.

SUBJECT'S IDENTIFICATION (I.D. plate or give name - last, first, middle)

Subject Name: \_\_\_\_\_ Subject # \_\_\_\_\_  
 Participating Investigator: \_\_\_\_\_ Date:     /     /      
Mo Day Yr  
 VAMC Name: \_\_\_\_\_ VAMC # \_\_\_\_\_  
*Prostate Cancer Intervention Versus Observation Trial (PIVOT):*  
 Title of Study: A Randomized Trial Comparing Radical Prostatectomy Versus Palliative Expectant  
Management for the Treatment of Clinically Localized Prostate Cancer - CSP #407

**Surgical treatment of CAP:** Surgical treatment of prostate cancer (prostatectomy) involves removing the prostate gland and nearby lymph nodes that may contain cancer. In men with prostate cancer that has not spread out of the prostate gland and who have had a radical prostatectomy, the chances of dying from prostate cancer within 10 years is 15%. In men whose prostate cancer has spread to other organs including lymph nodes, the chances of dying from prostate cancer after 10 years is 85%. Some doctors think that since these chances are so different, that if the cancer is discovered early and removed by surgery before it spreads, a man will be "cured." Surgery is believed to be especially likely to remove the cancer if the prostate cancers are small and slowing growing. However, most of these men would ordinarily die from some cause other than their prostate cancer anyhow. There would be no benefit from surgery but these men would still suffer the risks of surgery. Therefore, these men might do just as well using expectant management.

Surgery is also performed in some men who have prostate cancer that is large or fast growing because these men have a high risk of dying from prostate cancer. However, men with large or fast growing prostate cancer have a high probability that the cancer will reappear even after the prostate is surgically removed. They are unlikely to be "cured" by surgery. Even when the surgeon believes all the cancer has been removed, 40% of these men will have cancer reappear after 10 years. These men will have faced the risks of surgery without the benefit of cure.

Only one study has directly compared the results of men treated with radical prostatectomy with those treated with expectant management. In that small study there was no difference in survival at 15 years between the men treated with prostatectomy or with expectant management.

**Radiation treatment of CAP:** Radiation therapy is also used for treatment of CAP. However, previous studies indicate that men treated with radiation have a higher rate of cancer reappearing than men treated with prostatectomy. Therefore, radiation therapy is generally reserved for men who are poor surgical candidates or have disease beyond the prostate gland. Complications from radiation are similar to prostatectomy and include incontinence, impotence and colostomy. Death due to radiation therapy occurs in less than 0.5% of patients. We have not included radiation therapy as a separate treatment group. Radiation therapy is an option if you decline to enter this study.

**PROCEDURES:** If you agree to take part in this study, you will be assigned by chance to receive either Radical Prostatectomy or Expectant Management.



Subject Name: \_\_\_\_\_ Subject # \_\_\_\_\_

Participating Investigator: \_\_\_\_\_ Date: \_\_\_/\_\_\_/\_\_\_  
Mo Day Yr

VAMC Name: \_\_\_\_\_ VAMC # \_\_\_\_\_

Title of Study: Prostate Cancer Intervention Versus Observation Trial (PIVOT):  
A Randomized Trial Comparing Radical Prostatectomy Versus Palliative Expectant  
Management for the Treatment of Clinically Localized Prostate Cancer - CSP #407

**Treatment by Radical Prostatectomy.** If you are assigned to the radical prostatectomy group you could have up to two surgical procedures. You will be hospitalized for a prostatectomy within six weeks. Many surgeons first remove the lymph nodes from near the prostate gland (pelvic lymph node surgery). The pathologist will examine the lymph nodes for cancer cells. Some surgeons, however, do not remove the lymph nodes first and proceed with the prostatectomy as described below. Your surgeon will explain which method he/she uses.

If the lymph nodes do not contain cancer, you will receive a prostatectomy at the time of or within two weeks following the pelvic lymph node surgery. The procedure includes the removal of the entire prostate gland and the pouches that produce the seminal fluid (seminal vesicles) including the part of the urethra that passes through the prostate.

If your lymph nodes do contain cancer, you may not receive a prostatectomy because the cancer has spread outside of your prostate. Your doctor will discuss therapy options with you. These options are all part of current clinical practice and are not considered experimental. In general, they consist of radiation therapy, hormone therapy by pill, removal of the testicles, chemotherapy, mechanical interventions to open blocked passages in your bladder or kidneys, or expectant therapy to await disease progression or symptoms if they should occur.

If your disease returns, is not completely eliminated, or worsens, your doctor will provide you with other treatment options that are considered part of current clinical practice.

**Treatment by Expectant Management.** If you are assigned to the expectant management group you will not receive either a lymph node dissection or radical prostatectomy. Therefore, there will be no attempt to completely remove the cancer. Instead, you will be closely observed in a similar manner to the radical prostatectomy group. If the cancer does not spread to other organs or cause symptoms, no further treatment will be necessary. If the cancer causes symptoms, treatment will be aimed at providing relief of these symptoms. Symptoms that may be due to spread of prostate cancer are: blood in the urine, decrease in urine stream, swelling of the legs, pain in your pelvis, pain in other organs or bones, fatigue. Your doctor will closely examine you to determine if these symptoms are due to prostate cancer. Additionally, treatment will be provided if tests demonstrate that the cancer has spread to the bone or to other organs of the body even if you do not have symptoms. These treatments may consist of mechanical, radiation, hormonal, chemotherapy, or rarely prostatectomy as described above. All of these treatment methods are part of current clinical practice. The primary goal of the expectant management arm is to minimize treatment side effects while providing relief of cancer related symptoms. The expectant management treatment cannot completely remove the cancer nor is it able to cure the cancer.



Subject Name: \_\_\_\_\_ Subject # \_\_\_\_\_  
 Participating Investigator: \_\_\_\_\_ Date: \_\_\_/\_\_\_/\_\_\_  
Mo Day Yr  
 VAMC Name: \_\_\_\_\_ VAMC # \_\_\_\_\_  
 Title of Study: Prostate Cancer Intervention Versus Observation Trial (PIVOT):  
A Randomized Trial Comparing Radical Prostatectomy Versus Palliative Expectant  
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**Study Visits.** If you join the study you will have check-ups by your physician at weeks 6 and 12 following entry, then at six months and every six months for the remainder of the study (15 years total). At these check-ups your physician will look for any evidence of cancer by performing a rectal examination, blood tests (including prostate specific antigen [PSA]) and an annual bone scan. The results of all of these tests will be made available to you if your doctors think further treatment is necessary.

**RISKS AND INCONVENIENCES**

**Radical prostatectomy:** As outlined above, radical prostatectomy offers potential complete removal of prostate cancer. However, it may be neither effective nor necessary. Additionally, there are risks and possible complications to surgery. All men in the radical prostatectomy group will have an operation to remove the pelvic lymph nodes. Possible complications include bleeding, infection, or accumulation of tissue fluid (lymphocele) at the operative site, swelling of the legs and, extremely rarely, death.

Possible complications resulting from surgery to remove the prostate gland for men treated with radical prostatectomy alone are strictures (narrowing) of the bladder and/or urethra (8-14%), loss of bladder control (total urinary incontinence 6-10%, partial incontinence 10-25%), or loss of erection of the penis (impotence). Your doctor will do your surgery in a way that saves the nerves necessary for erection if the tumor can still be completely removed. Removing the tumor has priority over saving the nerves. If your doctor performs the surgery to save nerves for erection the risk of impotence is less than 50%. If your doctor does not use nerve saving surgery to remove your prostate the risk of impotence may be as high as 100%. These complications are usually temporary but may be permanent in 5-25% of men. Injury to the rectum requiring additional surgery to repair or remove occurs in 1-3% of men. Death due to surgery occurs in 1% of men.

**Expectant management:** Expectant management reserves therapy until prostate cancer causes symptoms or spreads to other organs. It also emphasizes treatment primarily directed at relieving the symptoms while minimizing side effects of treatment. Therapy in men in the expectant management group will not be necessary if prostate cancer does not cause symptoms or spread to other organs. Therefore, complications and side effects from treatment should be less in the expectant therapy than the prostatectomy group. However, the expectant therapy strategy does not provide the potential for complete removal of prostate cancer. Treatment reserved for symptoms cannot be guaranteed to always be effective. It is possible that if radical prostatectomy had been performed that CAP would have been completely removed and that you would have lived longer.

Subject Name: \_\_\_\_\_ Subject # \_\_\_\_\_

Participating Investigator: \_\_\_\_\_ Date:     /     /      
Mo Day Yr

VAMC Name: \_\_\_\_\_ VAMC # \_\_\_\_\_

Title of Study: Prostate Cancer Intervention Versus Observation Trial (PIVOT):  
A Randomized Trial Comparing Radical Prostatectomy Versus Palliative Expectant  
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**Additional evaluations, tests and procedures:** All tests performed in this study are considered routine and are a standard part of clinical practice for men with prostate cancer. These tests include a rectal and general physical examination, blood tests, x-rays and bone scans to determine if prostate cancer has recurred or spread. Radiation exposure and the amount of blood obtained for these tests are minimal.

**EXPECTED BENEFITS OF THE STUDY**

The frequent visits you will have during the study with a health care professional will afford you more intense medical follow-up than usual. You will receive frequent counseling and information about prostate cancer. The results of this study will allow us to determine the better treatment approach among these two options in men with prostate cancer.

**ALTERNATIVE COURSE OF ACTION**

If you choose not to participate in this study you will continue to receive the medical care which your doctor feels is most appropriate. This may be surgery, radiation or expectant therapy.

**USE OF RESEARCH RESULTS**

The results of this study will be used for scientific presentations and publications. You will never be identified in any way in any such presentations or publications.

By your consent to participate in this research study, you give up any property rights you may have in your bodily fluids, substances or tissues.

**WITHDRAWAL**

If you decide not to participate in this study, your decision will not affect the quantity or quality of care to which you are entitled. If you decide to participate, you will be free to withdraw at any time without prejudice. Withdrawal would not in any way affect the nature of the care or treatment otherwise available to you.



Subject Name: \_\_\_\_\_ Subject # \_\_\_\_\_

Participating Investigator: \_\_\_\_\_ Date:     /     /      
Mo Day Yr

VAMC Name: \_\_\_\_\_ VAMC # \_\_\_\_\_

Title of Study: Prostate Cancer Intervention Versus Observation Trial (PIVOT):  
A Randomized Trial Comparing Radical Prostatectomy Versus Palliative Expectant  
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**RESEARCH SUBJECTS' RIGHTS:** I have read or have had read to me all of the above.

Dr. \_\_\_\_\_ has explained the study to me and answered all of my questions. I have been told of the risks or discomforts and possible benefits of the study. I have been told of other choices of treatment available to me.

**I understand that I do not have to take part in this study, and my refusal to participate will involve no penalty or loss of rights to which I am entitled. I may withdraw from this study at any time without penalty or loss of VA or other benefits to which I am entitled.**

The results of this study may be published, but my records will not be revealed unless required by law.

In case there are medical problems or questions, I have been told I can call:

Dr. \_\_\_\_\_ at \_\_\_\_\_ during the day, and

Dr. \_\_\_\_\_ at \_\_\_\_\_ after hours.

If any medical problems occur in connection with this study the VA will provide emergency care.

**I understand my rights as a research subject, and I voluntarily consent to participate in this study. I understand what the study is about and how and why it is being done. I will receive a signed copy of this consent form.**

\_\_\_\_\_  
Subject's Signature

\_\_\_\_\_  
Date

\_\_\_\_\_  
Signature of Subject's Representative\*

\_\_\_\_\_  
Subject's Representative (print)

\_\_\_\_\_  
Signature of Witness

\_\_\_\_\_  
Witness (print)

\_\_\_\_\_  
Signature of Investigator

\*Only required if subject is not competent.

**APPENDIX B**  
**STUDY BUDGET**  
**POSITION DESCRIPTIONS**



VA COOPERATIVE STUDY 407  
 Prostate Cancer Intervention Versus Observation Trial (PIVOT): A Randomized Trial Comparing Radical  
 Prostatectomy Versus Palliative Expectant Management for the Treatment of Clinically Localized Prostate Cancer

Study Budget

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6	Year 7
Chairman's Office							
Personnel:							
Study Coord., GS-11	43,710	45,895	48,190	50,600	53,130	55,786	58,575
Program Asst., GS-5	23,842	25,034	26,285				
Equipment:							
fax machine	2,500						
(2) PC's, (1) printer	7,000						
Other Operating Costs:							
office supplies, etc.	2,000	2,000	2,000	1,500	1,500	1,500	1,500
Total	79,052	72,929	76,475	52,100	54,630	57,286	60,075
Participating Centers							
Costs for Enrollment							
12 monthly logs @\$150	1,800	1,800	1,800				
75 pts watching videotape							
@\$50/patient	3,750	3,750	3,750				
10 pts randomized @\$1,000 ea	10,000	10,000	10,000				
Costs for Follow-up							
\$400/yr for pt follow-ups (450	4,000	8,000	12,000	12,000	13,500	13,500	13,500
for Yrs 5-9, 500 for Yrs 10-15)	1,200	1,200	1,200				
Other Operating Costs							
Total	20,750	24,750	28,750	12,000	13,500	13,500	13,500
Total x 45 VA Centers	933,750	1,113,750	1,293,750	540,000	607,500	607,500	607,500
Linear Videotaping Costs	50,544						
*CSPCRPCC Central PSA Lab	191,168	121,766	147,872	121,681	117,801	115,098	122,938
Non-VA Central Pathology Lab	n/c	n/c	n/c				
CSPCC Beyond Core Costs							
Project Manager, GS-9	36,125	37,931	39,827	41,819	43,910	46,105	48,410
Computer Assistant, GS-6	26,575	27,904	29,299	30,764	32,303	33,918	35,614
Total	62,700	65,835	69,126	72,583	76,213	80,023	84,024
<b>TOTAL</b>	<b>1,317,214</b>	<b>1,374,280</b>	<b>1,587,223</b>	<b>786,364</b>	<b>856,144</b>	<b>859,907</b>	<b>874,537</b>

STUDY BUDGET (Cont.)

	Year 8	Year 9	Year 10	Year 11	Year 12	Year 13	Year 14
Chairman's Office Personnel: Study Coord., GS-11 Program Asst., GS-5 Equipment: fax machine (2) PC's, (1) printer Other Operating Costs: office supplies, etc. Total	61,504  1,500 63,004	64,579  1,500 66,079	67,808  1,500 69,308	71,199  1,500 72,699	74,759  1,500 76,259	78,497  1,500 79,997	82,422  1,500 83,922
Participating Centers Costs for Enrollment 12 monthly logs @\$150 75 pts watching videotape @\$50/patient 10 pts randomized @\$1,000 ea Costs for Follow-up \$400/yr for pt follow-ups (450 for Yrs 5-9, 500 for Yrs 10-15) Other Operating Costs Total Total x 45 Centers	    13,500 13,500 607,500	    13,500 13,500 607,500	    15,000 15,000 675,000	    15,000 15,000 675,000	    15,000 15,000 675,000	    15,000 15,000 675,000	    15,000 15,000 675,000
Linear Videotaping Costs							
*CSPCRPCC Central PSA Lab	163,371	118,027	161,799	119,076	116,108	128,983	121,840
Non-VA Central Pathology Lab							
CSPCC Beyond Core Costs Project Manager, GS-9 Computer Assistant, GS-6 Total	50,831 37,394 88,225	53,373 39,264 92,637	56,041 41,227 97,268	58,843 43,289 102,132	61,786 45,453 107,239	64,875 47,726 112,601	68,119 50,112 118,231
<b>TOTAL</b>	<b>922,100</b>	<b>884,243</b>	<b>1,003,375</b>	<b>968,907</b>	<b>974,606</b>	<b>996,581</b>	<b>998,993</b>

STUDY BUDGET (Cont.)

	Year 15	Year 16	TOTAL
Chairman's Office			
Personnel:			
Study Coord., GS-11	86,543	45,435	988,632
Program Asst., GS-5			75,161
Equipment:			
fax machine			2,500
(2) PC's, (1) printer			7,000
Other Operating Costs:			
office supplies, etc.	1,500	500	24,500
Total	88,043	45,935	1,097,793
Participating Centers			
Costs for Enrollment			
12 monthly logs @\$150			5,400
75 pts watching videotape			11,250
@\$50/patient			30,000
10 pts randomized @\$1,000 ea			
Costs for Follow-up			
\$400/yr for pt follow-ups (450	15,000		193,500
for Yrs 5-9, 500 for Yrs 10-15)			3,600
Other Operating Costs			243,750
Total	15,000		10,968,750
Total x 45 Centers	675,000		
Linear Videotaping Costs			50,544
*CSPCRPCC Central PSA Lab	114,695		1,982,223
Non-VA Central Pathology Lab			
CSPCC Beyond Core Costs			
Project Manager, GS-9	71,525	37,550	817,070
Computer Assistant, GS-6	52,618	27,624	601,084
Total	124,143	65,174	1,418,154
TOTAL	1,001,881	111,109	15,517,464

Patient Recruitment: 3 years Salary projections based on General Schedule effective January 1993,  
 Follow-up: 12 years plus 30% fringe and a 5% increase each year.  
 Participating VA Centers: 45 \*Cost of assay kits are included in PSA Lab cost. \$723,568 will be saved if kits are donated.

PROJECT COORDINATOR (GS-11) 1.0 Chairman's Office

**Principal Duties and Responsibilities**

1. The incumbent serves as the Staff Assistant to the Chairman's Office for VA Cooperative Study #407, "Prostate cancer Intervention Versus Observation Trial (PIVOT)". This is a 15 year study in which 80 Medical Centers (45 VAMC and 35 NCI-MC) recruit 2000 patients into the trial. The budget exceeds \$10 million. The incumbent will serve as contact between the Study Chairman and Perry Point CSPCC the 45 participating VAMC and the 35 NCIMC, working independently most of the time.
2. Major responsibilities include initiation, evaluation, and management of all administrative functions of the Chairman's Office for Cooperative Study #407. Specifically, this involves key responsibilities for overall budget planning and implementation, resource allocation, staff review, preparation and submission of annual budget plan, and position description development for personnel involved in the study.
3. The incumbent serves as principal liaison between the participating stations and the Chairman's Office, the Cooperative Studies Central Offices in Boston and Washington, the Coordinating Center in Perry Point, the Central Pathology Laboratory, the Co-Chairman's Office in Seattle and study group and committee members.
4. The incumbent monitors the performance of study participants as to patient accrual, completeness and timeliness of patient data, and management of funding. He/she recognizes complications in the study and brings them to the attention of the Study Chairman.
5. The incumbent organizes and plans the study meetings of the standing committees and of the study group including selection of dates, development of agenda, coordination of travel plans, and funding requests according to CSP guidelines.
6. The incumbent develops and maintains records of patient accrual, analysis of deaths, and protocol breaches.
7. The incumbent works closely with the Perry Point Coordinating Center and Study Chairman in various analyses of the data.
8. The incumbent reviews all data from the 80 participating centers for completeness and accuracy and makes whatever corrections are necessary in consultation with the appropriate study personnel.
9. The incumbent prepares and meets deadlines for study reports as required by the Perry Point Coordinating Center, the national Cooperative Study Guidelines, the Data Monitoring Board, the Human Rights Committee, and other bodies.
10. The incumbent will be responsible for maintaining patient files containing study forms, appropriate reports and consent forms, on all patients entered into the study, which will number approximately 2000 for this study.
11. The incumbent handles budgetary and logistic aspects of Central Pathology Laboratory relationship with the 80 centers and the Chairman's office and ensures that all specimens are received and read by the Central Laboratory.

12. The incumbent assists the Study Chairman in developing performance standards and job descriptions for research coordinators.

13. The incumbent is responsible for setting up a contractual arrangement with the three physicians chosen to serve on the endpoints committee. He/she is responsible for sending these individuals reports of death or other endpoints and assuring that they act upon these reports in a timely and complete manner.

14. The incumbent assists in preparing Cooperative Study Program and any other grant applications, including formulating budget justifications and bibliographies.

### **Knowledge Required by Position**

1. A thorough working knowledge of the guidelines and regulations associated with the administration of VA-funded research proposals, specifically Cooperative Studies.

2. Thorough knowledge of the Study Protocol, Operations Manual and Research Data Forms for CSP #407. He/she shall understand the objectives of the Study as well as its organization, procedural rules, personnel, material, etc. needed to achieve the Study objectives.

3. Experience in administrative and medical or health-related fields is required.

4. Knowledge and insight is necessary to maintain an accurate data management control system for recording and reviewing all patient data information in order to provide timely information on status and progress of the Study.

5. Knowledge of the administrative functions of the Study Chairman's Office.

6. Knowledge of English grammar, spelling and punctuation to compose error free correspondence and study related manuscripts, abstracts and newsletters.

7. Knowledge to assist in accruing and compiling data statistics for completion of quarterly and annual reports for the Cooperative Study Program. Data needed for reports may have to be extracted from various sources and compiled into a comprehensive format for analysis.

8. Ability to control and balance research funding allotments.

9. Ability to effectively deal with communications of a substantially research/clinical nature from participants and support personnel.

10. The incumbent must demonstrate reliability, independence, and originality in solving problems in the Chairman's absence.

### **Supervisory Controls**

Authority and responsibility is delegated to the Staff Assistant by the Study Chairman to plan, develop, and direct all activities associated with the professional conduct and successful completion of the Study. The Staff Assistant regularly advises the Study Chairman regarding operating difficulties and other problems associated with the execution of the Study such as lagging patient accrual, breaches of protocol, and patient complications. The incumbent will work with a high degree of independence and completed work is relied on for accuracy.



## PROGRAM ASSISTANT (GS-5) I.O Chairman's Office

1. The incumbent serves as the Program Assistant to the Chairman's Office during the three years of participant enrollment for VA Cooperative Study #407, "Prostate cancer Intervention Versus Observation Trial (PIVOT)". This is a 15 year study in which 80 Medical Centers (45 VAMC and 35 NCI-MC) recruit 2000 patients into the trial. The incumbent will assist the Project Coordinator and Chairman in contacts between the Study Chairmen and Perry Point CSPCC the participating VAMC and the NCIMC.
2. Major responsibilities include secretarial assistance with all administrative functions of the Chairman's Office for Cooperative Study #407 as defined in the PD for the Project Coordinator. Specifically, this involves telephone contacts, preparation of memos, collecting and monitoring data forms and delivery of laboratory specimens.
3. The incumbent assists the Project Coordinator as a liaison between the participating stations and the Chairman's Office, the Cooperative Studies Central Offices in Boston and Washington, the Coordinating Center in Perry Point, the National Cancer Institute, the Central Pathology Laboratory, the Co-Chairman's Office in Seattle, and study committee members.
4. The incumbent helps the Staff Assistant in monitoring the performance of study participants as to patient accrual, completeness and timeliness of patient data and in preparing Cooperative Study Program and any other grant applications, including formulating budget justifications and bibliographies.
5. The incumbent collects data for the Project Coordinator's review from study centers.

### **Knowledge Required by Position**

1. Experience in word processing and telephone communications is required. Experience in the medical or health-related fields is desired.
2. Experience in maintaining organized study related files and correspondence.
3. Knowledge of the administrative functions of the Staff Assistant to the Chairman.
4. Knowledge of English grammar, spelling and punctuation to compose error free correspondence and study related manuscripts, abstracts and newsletters.

### **Supervisory Controls**

The Program Assistant is directly responsible to the Chairman. However, the incumbent will work closely with the Project Coordinator to coordinate much of the daily duties that are required for successful completion of the study.

### **Personal Contacts**

Establishes and maintains a liaison with various division of the local medical center as well as the Coordinating Center, the participating centers, the Co-Chairman's office, and the Central Pathology Laboratory. The Program Assistant has the ability to maintain effective relationships while maintaining tact, poise, resourcefulness, judgment and the ability to gain cooperation.

### **Physical Demands**

No special physical demands are required to perform the work.



DEPARTMENT OF VETERANS AFFAIRS  
Medical Center  
2100 Ridgecrest Drive SE  
Albuquerque NM 87108

VA COOPERATIVE STUDIES PROGRAM CLINICAL  
RESEARCH PHARMACY COORDINATING CENTER (151-I)

July 30, 1993

In Reply Refer To: 501/151-I  
CSP #95/#407  
File: C

David G. Weiss, Ph.D.  
CSPCC (151-I)  
VA Medical Center  
Perry Point, MD 21902

THRU: Chief, CSPCC Perry Point

SUBJ: CSPCRPCC Biopharmaceuticals/Pharmacokinetics Laboratory Materials for CSP #407.

1. Enclosed is the proposed budget for the Albuquerque Biopharmaceuticals/Pharmacokinetics Laboratory (BPL) to perform prostate specific antigen analysis (PSA) for CSP #407. "Prostate Cancer Intervention Versus Observation Trial".

2. The budget is based on the assumption that there will be 80 participating sites and the duration of the study will be 15 years. Other assumptions are stated as part of the budget justification.

JAMIE G. BARNHILL, Ph.D  
Chief, Biopharmaceuticals/Pharmacokinetics Laboratory  
VA Cooperative Studies Program  
Clinical Research Pharmacy Coordinating Center

CONCUR:

MIKE R. SATHER, M.S., F.A.S.H.P.  
Chief, VA Cooperative Studies Program  
Clinical Research Pharmacy Coordinating Center

Enclosures

**CSPCRPCC BIOPHARMACEUTICS/PHARMACOKINETICS LABORTORY  
ASSUMPTIONS AND JUSTIFICATIONS FOR CSP #407**

1. Blood drawing supplies for participating sites have been included in the budget. These items may be part of the standard supplies found in the clinics.
2. It is assumed that each of the 80 sites will have access to centrifuge for spinning the blood samples for collection of the serum.
3. It is assumed that each participating site will have suitable freezer space to store the serum samples until the time of each monthly shipment. During the year with the greatest number of subjects expected to participate, the average is approximately 7, so the number of tubes requiring storage and the total size of needed storage is very small.
4. It is assumed that each participating site will have access to dry ice for shipment of the serum samples in the insulated mailers.
5. Most supplies have been budgeted to be purchased in large quantities at only a few points in time. Those items that are required to be sterile and those items that are large and require plenty of storage space are budgeted to be purchased at more frequent intervals.
6. All supplies have been calculated with a 4% yearly increase to offset inflation.
7. Insulated mailers have been budgeted for each participating site each month of the study. It is possible to reuse the mailers, however this requires the VA CSPCRPCC to mail the containers back to each location. This would require additional monies to be added to the "Shipping Costs" portion of the budget.
8. Two ultra-low temperature freezers have been requested. One will be located in the warehouse area of the CRPCC and one will be located inside the BPL. Each is equipped with a chart recorder, alarm, racks, and CO2 backup. The life span of these types of freezers is ten years therefore, funding is requested for two new freezers in year ten. The prices reflect a 4% yearly increase in cost.
9. An Abbot IMX analyzer is requested for performing the PSA assays. Funding is requested again in year eight for the replacement of the analyzer.
10. A computer is requested in year one for data handling and tracking.
11. Funds have been requested to offset maintenance, service and repair on the freezers and analyzer.
12. A GS-8 chemist/technician is requested. The duties of this individual will include (but are not limited to) conducting the PSA assays, performing the routine maintenance and calibration on the equipment, maintaining the data, coordinating the arrival, transfer and log-in of samples, and preparing the data reports.
13. The budget is calculated assuming the PSA kits will be donated. The purchase price to the VA for each PSA kit would be \$656. The total cost for the kits, should they have to be purchased, is indicated under the section, "SUPPLIES - Assay."

**CSPCRPCC BIOPHARMACEUTICS/PHARMACOKINETICS LABORATORY  
SAMPLE HANDLING PROTOCOL FOR CSP #407**

Blood samples will be obtained by venipuncture using vacuum redtop tubes. The sample should be allowed to coagulate and is then spun in a centrifuge to separate the serum from the clot. The stopper should then be gently removed and two 2ml aliquots should be pipetted into labeled storage tubes. The tubes should then be frozen until the time of shipping. Storage tubes, labels, and disposable pipettes will be provided.

Once monthly, or more frequently if necessary, all samples should be gathered together, placed into the insulated mailer, surrounded by dry ice, carefully sealed, and shipped to the VA CSPCRPCC by overnight mail.

At the CRPCC, the packages will be checked, logged-in, and the contents will be placed into one of the ultra-low temperature freezers. At weekly intervals, the duplicate samples will be separated and one portion will be transported to the Biopharmaceutics/Pharmacokinetics Laboratory (BPL) on ice.

At the BPL, the samples will be logged-in, issued a chain-of-custody document, and placed into the appropriate location in an ultra-low temperature freezer.

At period intervals, the subjects serum will be removed for determination of PSA levels. At that time, the samples will be brought to room temperature and gently mixed. Duplicate 150 ul aliquots will be tested.

CSPCRPCC BIOPHARMACEUTICS/PHARMACOKINETICS LABORATORY  
 BUDGET FOR CSP# 407  
 AUGUST 2, 1993

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6	Year 7	Year 8	Year 9	Year 10	Year 11	Year 12	Year 13	Year 14	Year 15	TOTAL
<b>PERSONNEL</b>																
Technician/Chemist	31,449	35,797	34,283	38,915	40,094	43,366	45,101	48,285	50,216	51,652	53,717	55,866	62,104	64,338	67,171	772,604
GS-3 (1.0 FTR)																
Institute 25 S																
Fringe Benefits																
<b>SUPPLIES</b>																
Blood Drawings																
1. Red-top Tubes	1,770	2,118			1,448		1,736		1,609		1,741		1,569		543	12,778
2. Needles	1,268	1,516			1,311		1,242		1,343		1,655		1,073		341	9,189
3. Halden	339			370			404			471			528			2,113
4. Swabs	384			322			265			296			360			1,579
5. Trenchants	1,650				825					825						3,300
6. BandAids	1,020			745			680			595			518			3,576
<b>Sample Reagents</b>																
1. Disposable Pipette	664			575			555			536			449			2,799
2. Sample Storage Tubes	4,990			4,400			4,091			4,117			3,543			21,081
3. Tube Labels	800					800					800					2,400
<b>AMST</b>																
1. Pipette Tips	600				720					600						1,920
2. Calibration and Control Samples and Diluter	620	643	671	697	725	754	784	815	848	882	917	954	992	1,032	1,073	12,409
3. <PRA Eto>	<49,856>	<49,536>	<49,216>	<47,872>	<45,792>	<43,168>	<40,544>	<36,576>	<33,952>	<32,640>	<30,016>	<28,048>	<26,080>	<24,112>	<22,960>	<723,548>
<b>Printer Reagents</b>																
1. Divided Beams	1,756									1,756						3,512
2. Receiver Charts	190			190			190			190			190			950
<b>Shipping Costs</b>																
1. Insulated Holders	6,912	7,188	7,476	7,775	8,064	8,410	8,746	9,095	9,459	9,837	10,230	10,640	11,065	11,508	11,967	138,394
2. Overweight at 210/pkg and over monthly shipments	9,600	9,600	9,600	9,600	9,600	9,600	9,600	9,600	9,600	9,600	9,600	9,600	9,600	9,600	9,600	144,000
<b>EQUIPMENT</b>																
1. Ultra-Low Temp. Freezer (7) with alarm, receiver, rack, and CD3 backup	25,160									36,100						61,260
2. Abbott DCC Analyzer	48,000							48,000								96,000
3. Computer	2,500															2,500
4. Service/Installation/Upgrade	1,000	1,000	1,000	1,000	1,000	1,000	1,000	1,000	1,000	1,000	1,000	1,000	1,000	1,000	1,000	15,000
<b>TOTAL</b>	141,312	21,220	51,658	64,609	64,009	63,920	74,394	116,795	74,073	119,159	79,069	78,060	97,903	87,728	91,725	1,238,655

<> Not included in total.

**APPENDIX C**  
**CURRICULA VITAE**



**CURRICULUM VITAE**  
**Timothy James Wilt, M.D., M.P.H.**

**Personal Data:** Section of General Medicine Minneapolis VA Medical Center/1110  
One Veterans Drive Minneapolis, Minnesota 55417  
(612) 725-2000 ext. 2681 Fax: (612) 725-2118

**Education:** 1974-1978 The Colorado College, Colorado Springs, CO - B.A. Chemistry  
1978-1983 University of Illinois College of Medicine - M.D.

**Postgraduate Training:** 1983-1986 Internship and Residency in Medicine,  
University of Minnesota, Minneapolis, MN  
1987-1990 Masters in Public Health, University of Minnesota,  
Graduate School of Public Health

**Academic Positions:** 1986-1987 Chief Medical Resident, Minneapolis VAMC Minneapolis, MN  
1987-1990 Clinical Instructor University of Minnesota, MVAMC  
1990 Assistant Professor of Internal Medicine  
University of Minnesota, MVAMC, Minneapolis, MN

**Honors:** 1979 College of Medicine Summer Research Fellowship  
1979-83 James Scholar Program for Independent Study in Medicine  
1981 Bertram Richardson Scholarship for Overseas Studies  
1982 Richard Muldovsky Scholarship for Excellence in Physiology  
1983 Medical Student Research Forum First Place Award  
1986-87 Chief Medical Resident, MVAMC, Minneapolis, Minnesota

**Board Certification:** 1986 American Board of Internal Medicine

**Licensure:** 1984- State of Minnesota #029677 5

**Professional Organizations:** Phi Beta Kappa; American Chemical Society; American College of Physicians; Society for General Internal Medicine

**Teaching/Administrative Positions:** \* Chief Medical Resident, Minneapolis VAMC (1986-87)  
\* Director Admissions Area, MVAMC (1987-90)  
\* Co-director General Medicine Walk-in Clinic, MVAMC (1987-90)  
\* Director General Internal Medicine Fellowship Program (1989-present)  
\* Director Medical Preoperative Clinic (1989-92)  
\* Director Medicine Residents Ambulatory Care Rotation (1989-92)  
\* Member: Professional Standards Board MVAMC 1991-92  
\* Staff Physician General Medicine Section; MVAMC

**Research: Epidemiology and Prevention of Chronic Diseases**

- \* Co-principal Investigator: Minneapolis Center; Multicenter Isradipine/Diuretic Atherosclerosis Study.
- \* Principle Investigator: Peripheral Vascular Disease in patients in MIDAS.
- \* Co-Investigator: Cholesterol and Recurrent Events (CARE).
- \* Principal Investigator: Peripheral Vascular Disease in the CARE Study.
- \* Principal Investigator: MVAMC site VA Cooperative Study #363: HDL Intervention Trial (HIT).
- \* Principal Investigator: Peripheral Vascular Disease in the HDL Intervention Trial (HIT).
- \* Co-principal Investigator/Project Director: NHLBI-RFP. Arterial Diseases Multi-Intervention Trial.
- \* Chairman: VA Cooperative Study #407. Prostate Cancer Intervention versus Observation trial (PIVOT).



**Previous Grants:**

- Minnesota Medical Foundation: Effect of Fish Oil on hypercholesterolemic men. Co-principal Investigator; \$7900 (1987-88).
- Program grant for Fellowships in Ambulatory Care. Department of Veterans Affairs funded: Program Director: \$120,000 (1990-92)

**Active Grants:**

- Multicenter Isradipine Diuretic and Atherosclerosis Study (MIDAS). Co-Investigator: \$3,000,000 (1989-94) Sandoz Corporation.
- Peripheral Arterial Disease MIDAS. Principal Investigator: \$25,000 (1990-94) Sandoz.
- Program grant for Fellowships in Ambulatory Care. Program Director: \$240,000 (1992-6) Department of Veterans Affairs.
- High Density Lipoprotein Intervention Trial (HIT):VA Cooperative Trial #363. Principal Investigator Minneapolis Site; \$500,000 (1991-98) VA Cooperative Studies Program.
- Ultrasound detection and evaluation of peripheral vascular disease in the HDL Intervention Trial: Principal Proponent; \$117, 000 (1992-98). VA Cooperative Studies Program.
- Peripheral Arterial Disease: A pilot study to evaluate treatment and prevention strategies for atherosclerotic cardiovascular disease. Co-principal Investigator/project director; Minnesota site award: \$666, 202. (1992-1995) NIH (RFP# NHLBI-HC-92-11).
- Program grant for Education in Primary Care; Fellowship Program director. \$40,000 (1992-96). University of Minnesota Health Right Foundation.
- Observation versus prostatectomy for clinically localized carcinoma of the prostate. VA Cooperative Study #407. Approved for planning. Study Chairman. (1992-93) VA Cooperative Studies Program
- Detection and monitoring of femoral arterial plaque in the Cholesterol And Recurrent Events Study (CARE). Principal Investigator. \$97,800. (1993-96) Bristol Myer-Squibb

**Grants Submitted and Pending Approval:**

- Prostate Cancer Intervention Versus Observation Trial (PIVOT). VA/NCI Cooperative Study #407. (1993-2008)

## BIBLIOGRAPHY: Published Articles and Books

- 1) Wilt TJ, Lofgren RP, Nichol KL, Schorer AE, Crespín L, Downes D, Eckfeldt J. Fish Oil Supplementation Does Not Lower Plasma Cholesterol in Men with Hypercholesterolemia: Results of a randomized double blind controlled cross-over study. *Annals Int Med* 1989;111:900-905
- 2) The MIDAS Research Group. Multicenter Isradipine Diuretic Atherosclerosis Study (MIDAS): Design Features. *Am J Med* 1989;86:(4A)37-39.
- 3) Wilt TJ, Lofgren RP, Nichol KL, Eckfeldt J. Fish oil supplements do not treat hypercholesterolemia in middle aged men: *Cardiology Board Review*. 1991;8:80-89.
- 4) Wilt TJ and Cutler A. Physician Performance and Patient Perceptions during the Rectal Examination. *J Gen Int Med* 1991;6:514-517.
- 5) Sacks FM, Pfeffer MA, Moye L, et al for the CARE Investigators. Rationale and Design of a Secondary Prevention Trial of Lowering Normal Plasma Cholesterol Levels after Acute Myocardial Infarction: The Cholesterol and Recurrent Events Trial (CARE). *Am J Cardiol* 1991;68:1436-1446.
- 6) Wilt TJ. Evaluation and Management of Patients with Lower Extremity Peripheral Vascular Disease. *J Gen Int Med* 1992;7:87-101.
- 7) Rubins HB, Schectman G, Wilt TJ, Iwane M., Distribution of lipid phenotypes in Community-Living Men with Coronary Heart Disease. *Archives Int Med* 1992; 152:2412-2416.
- 8) Rubins HB, Robins SJ, Iwane MK, et al. Rationale and Design of the Department of Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial (HIT) for Secondary Prevention of Coronary Artery Disease in Men with Low High-Density Lipoprotein Cholesterol and Desirable Low-Density Lipoprotein Cholesterol. *Am J Card* 1993; 7145-52.
- 9) Lofgren RP, Wilt TJ, Nichol KL, Crespín L, Pluhar R, Eckfeldt J. Effect of fish oil supplementation on blood pressure: Results of a randomized cross-over trial. *Am J Pub Health* 1993; 83:267-269.
- 10) Wilt TJ. Current Approaches to the Patient with Peripheral Vascular Disease. *Today in Medicine*. 1993;8:21-23.
- 11) Wilt TJ, Sprinkle J, Hass A, Heurer C, Applegate W, Schnaper H, Flack J, Borhani N and Grimm R. Prevalence and Correlates of Peripheral Vascular Disease in hypertensive patients with carotid atherosclerosis: Baseline results from the Multicenter Isradipine/Diuretic Atherosclerosis Study (MIDAS) *J Vasc Med and Bio*. 1993 in press.

## Letters

Wilt TJ, Lofgren RP, Nichol KL. Fish Oil Supplementation and Plasma Cholesterol: The Power of a Clinical Trial. *Ann Intern Med*. 1990; 112: 633-4.

Wilt TJ, Ensrud KE, Joseph AM. Milking the Prostate. *JAMA*. 1992; 268:3198-3199.

### Articles submitted for publication

Wilt TJ and Macpherson DS. Effectiveness of a medical preoperative clinic in a university affiliated medical center. (Submitted 1993).

Wilt TJ, Brawer MK Barry MJ et al. Clinical trials for localized prostate cancer are ethical, necessary and ongoing. (Submitted 1993).

Wilt TJ, Sacks F, Meyers D and Davis B. Prevalence and determinants of peripheral vascular disease in the CARE study. (Manuscript in preparation)

Nash DT, Davis B, Wilt TJ and Sacks F. Interrelationships between risk factors at Baseline of the CARE study. (Manuscript in preparation)

### Invited Lectures

Wilt TJ. Evaluation and Management of Peripheral Vascular Disease. MVAMC. July 1990.

Wilt TJ. Current Approaches to Patients with Peripheral Vascular Disease. United Medical Center, St. Paul, MN. August 1990.

Wilt TJ. Controversies in Performing the rectal examination. MVAMC. February 1991.

Wilt TJ. Medical Consequences of High Latitude and Altitude Travel. MVAMC, Mpls, MN. July 1991.

Wilt TJ. Screening for Carcinoma of the Prostate. MVAMC. Mpls, MN. December 1992.

Wilt TJ. Is their evidence to support early detection and Treatment of Prostate Cancer. United Medical Center, St. Paul, MN. March 1993.

### **Previous Fellows under Supervision of Dr. Wilt:**

1. Dr. William Conroy. Staff Physician, Park Nicollet Medical Center, Minneapolis, MN.
2. Dr. Jane Pederson. Ambulatory Care and Health Services Research Fellow, MVAMC.
3. Dr. Maureen Murdoch. General Internal Medicine and Epidemiology Fellow, MVAMC.
4. Dr. Christopher Goerd. Ambulatory Care and Epidemiology Fellow, MVAMC.
5. Dr. Cheryl Oncken. General Internal Medicine and Epidemiology Fellow, MVAMC.

## CURRICULUM VITA

MICHAEL K. BRAWER, M.D.  
Chief, Section of Urology  
VA Medical Center  
Seattle, WA

**Education:** B.S. University of California, Los Angeles, CA, 1975  
M.D. University of California, School of Medicine, Los Angeles, CA, Medicine, 1979

### Professional

**Experience:** 1991-Present Associate Professor, Urology, University of Washington, Seattle, WA  
Adjunct Associate Professor, Pathology, University of Washington, Seattle, WA  
1989-Present Chief, Section of Urology, Seattle Veterans Administration Medical Center, Seattle, WA  
1989-1991 Assistant Professor, Urology; Adjunct Assistant Professor, Pathology, University of Washington, Seattle, WA.  
1986-1989 Assistant Professor of Surgery (Urology), University of Arizona Health Sciences Center  
Staff Physician Surgery (Urology), Tucson Veterans Administration Medical Center, Tucson, AZ  
1985-1986 Chief Resident, Department of Surgery, Division of Urology, Stanford University School of Medicine, Stanford, CA  
1981-1982 Resident, Department of Surgery, Stanford University School of Medicine, Stanford, CA  
1980-1981 Intern, Department of Surgery, Stanford University School of Medicine, Stanford, CA

### Publications:

Andriole, G.L., Braver, M.K., Gerber, G.S. and Mettlin, C.: Prostate cancer screening. Cortland, Forum, 12/1992.

Braver, M.K.: Prostatic Intraepithelial Neoplasia: A Premalignant Lesion. J. of Cellular Biochemistry, 16G:171-174, 1992.

Braver, M.K., Ploch, N.R. and Bigler, S.A.: Prostate cancer tumor location as predicted by needle biopsy. J. of Cellular Biochemistry, 7/1992.

Braver, M.K. Bigler, S.A. and Deering, R.E.: Quantitative morphometric analysis of the microcirculation in prostate carcinoma. J. of Cellular Biochemistry, 7/1992.

Braver, M.K.: Relevance of PSA Continues to Unfold. In: Contemporary Urology 8/1992.

## **CURRICULUM VITA (Cont.)**

**MICHAEL K. BRAWER, M.D.**

### **Publications (Cont.):**

Brawer, M.K.: Prostatic Intraepithelial neoplasia: a premalignant lesion. *Hu. Path.*, 23:242-248, 1992.

Flam, T.A., Brawer, M.K., Cooper, E.H. and Nasser, J.: Diagnosis and markers in prostate cancer. *Cancer*, 70:357-358, 1992.

Brawer, M.K., Chetner, M.P., Beatle, J., Buchner, D.M., Vessella, R.L. and Lange, P.H.: Screening for prostatic carcinoma with prostate specific antigen. *J. Urol*, 147:841-45, 1992.

Pajouh, M.S., Nagle, R.B., Breathnach, R., Finch, J.S., Brawer, M.K. and Bowden, G.T.: Expression of metalloproteinase genes in human prostate cancer. *J. Cancer Res. Clin. Oncol.*, 117:144-150, 1991.

Petein, M., Michel, M. van Velthoven, R., Pasteels, J., Brawer, M.K., Davis, J.R., Nagle, R.B. and Kiss, R. Morphonuclear relationship between prostatic intraepithelial neoplasia (PIN) and cancers as assessed by digital cell image analysis. *Am. J. Clin. Path.* 96:628, 1991.

Sohlberg, O.E., Chetner, M.P., Ploch, N. and Brawer, M.K. Prostatic abscess after transrectal ultrasound-guided biopsy. *J. Urol* 146:420, 1991.

Brawer, M.K., Bigler, S.A., Sohlberg, O.E., Nagle, M.D. and Lange, P.H. Significance of prostatic intraepithelial neoplasia on prostate needle biopsy. *Urol.* 38:103, 1991.

Nagle, R.B., Brawer, M.K., Kittelson, J. and Clark, V. Phenotypic relationship of prostatic dysplasia (intraepithelial neoplasia) to invasive carcinoma. *Am. J. Pathology* 138:119, 1991.

Clark, R.L., Brawer, M.K., Hunter, G.C. and Pabst, T.S. Treatment of renal cell carcinoma by extracorporeal partial nephrectomy and autotransplantation utilizing splenic vascular anastomoses. *Surgery, Gynecology and Obstetrics* 175:105, 1991.

Brawer, M.K. Prostate specific antigen. *Acta Oncologica* 30:161, 1991.

Brawer, M.K. Implications of premalignant lesions of the prostate. *Contemporary Urology* 2:62, 1990.

Brawer, M.K. and Lange, P.H. Prostate specific antigen in the management of prostatic carcinoma. *Urology* 33:11, 1989.

Brawer, M.K. Prostatic intraepithelial neoplasia and prostate specific antigen. *Urology* 34:62, 1989.

## CURRICULUM VITA (Cont.)

MICHAEL K. BRAWER, M.D.

### Publications (Cont.):

Brawer, M.K., Rennels, M.A., Nagle, R.B., Solderer, M.H. and Lee, F. Prostatic intraepithelial neoplasia: a lesion which may be confused with cancer on prostatic ultrasound. *J. Urol.* 142:1510, 1989.

Brawer, M.K., Rennels, M.A., Nagle, R.B., Schifman, R.A. and Gaines, J. Serum prostate specific antigen and prostate pathology in men undergoing simple prostatectomy. *A. J. Clin. Path.* 92:760, 1989.

Brawer, M.K. and Lange, P.H. Prostate specific antigen and premalignant change: Implications for early detection. *Ca-A Journal for Clinicians* 39:361, 1989.

Brawer, M.K. and Lange, P.H. Transrectal ultrasonography of the prostate. *Western J. Med.* 151:448, 1989.

Lange, P.H. and Brawer M.K. Serum prostate specific antigen: Its use in diagnosis and management of prostate cancer. *Urol* 33:13, 1989.

Brawer, M.K. and Lange, P.H. PSA in the screening, staging and followup of early stage prostate cancer. A review of recent developments. *World J. Urol.* 7:7, 1989.

Brawer, M.K., Williams, W., Witte, C.L. and Bocchini, G.C., et al. Massive Lymphocele following pelvic lymphadenectomy for staging of prostatic cancer. *Lymphology* 22:36, 1989.

Brawer, M.K., Lange, P.H. Prostate Specific Antigen: its role in early detection, staging and monitoring of prostatic carcinoma. *Endourology* 3:227, 1989.

Fuchs, M.E. and Brawer, M.K., Rennels, M.A. and Nagle, R.B. The relationship of basement membrane to histologic grade of human prostate carcinoma. *Modern Path.* 2:105, 1989.

Fuchs, M.E. and Brawer, M.K. Papaverine Induced fibrosis of the corpus cavernosum. *J. Urol* 141:125, 1989.

Brawer, M.K., Nagle, R.B., Pitts, W., Freiha, F.S., and Gamble, S.L. Keratin Immunoreactivity as an aid to the diagnosis of persistent adenocarcinoma in irradiated human prostates. *Cancer* 63:454, 1989.

The above were selected from more than 100 publications.



## CURRICULUM VITA

DAVID G. WEISS, Ph.D.  
Medical Statistician  
Cooperative Studies Program  
Coordinating Center (151E)  
VA Medical Center  
Perry Point, MD 21902

- Education:** B.S. (Mathematics) Duquesne University Pittsburgh, PA, 1968  
M.S. (Biostatistics) Medical College of Virginia, Richmond, VA, 1972  
Ph.D. (Biostatistics) Medical College of Virginia, Richmond, VA, 1974
- Experience:** 1989-Present Assistant Chief, CSPCC, VAMC, Perry Point  
1974-Present Study Biostatistician, CSPCC, VAMC, Perry Point, MD  
1968-1969 Mathematician, Department of Interior, U.S. Bureau of Mines,  
Pittsburgh, PA
- Committees:** 1990-Present Chairman, Research and Development Committee, VAMC, Perry  
Point, MD  
1983-1987 Research and Development Committee, VAMC, Perry Point, MD  
1987-1989 Eastern Research and Development Office - Advisory Committee

### Professional

**Organizations:** American Statistical Association; President, Delaware Chapter  
Biometrics Society  
Society for Controlled Clinical Trials

### Publications:

Collins, J.F., Bingham, S.F., Weiss, D.G., Williford, W.O., and Kuhn, R.M.: Some adaptive Strategies for Inadequate Sample Acquisition in Veterans Administration Cooperative Clinical Trials. Controlled Clinical Trials, 1:227-248, 1980.

Niederman, R., Sullivan, T.M., Weiss, D.G., Morhart, R., Robbins, W., Maier, D.: Oral Hygiene Skill Index II. Journal of Periodontology, 52(3):150-154, March 1981.

Wertz, R.T., Collins, M.J., Weiss, D.G., Kurtzke, J.F., Friden, T., Brookshire, R.H., Pierce, J., Holtzapple, P., Hubbard, D.J., Porch, B.E., West, J.A., Davis, L., Matovich, V., Morley, G.K., Resurrection, E.: Veterans Administration Cooperative Study on Aphasia: A Comparison of Individual and Group Treatment. Journal of Speech and Hearing Research, 24:580-594, December, 1981.

Ling, W., Weiss, D.G., Charuvastra, V.C., O'Brien, C.P.: Use of Disulfiram for Alcoholics on Methadone Maintenance Programs. Archives of General Psychiatry, 40:851-854, August 1983.



## CURRICULUM VITA (Cont.)

DAVID G. WEISS, Ph.D.

### Publications (Cont.):

Weiss, D.G., Williford, W.O., Collins, J.F., and Bingham, S.F. Planning Multicenter Clinical Trials: A Biostatistician's Perspective. Controlled Clinical Trials, 4:53-64, 1983.

Weiss, D.G., Williford, W.O., Collins, J.F., and Bingham, S.F.: Training of Biostatisticians for Clinical Trials: A Survey: Proceedings of the Section on Statistical Education, American Statistical Association, Washington, DC, 16-21, 1983.

Collins, J.F., Williford, W.O., Weiss, D.G., Bingham, S.F., and Klett, C.J.: Planning Patient Recruitment: Fantasy and Reality. Statistics in Medicine, 3:435-443, 1984.

Williford, W.O., Bingham, S.F., Weiss, D.G., Collins, J.F., Rains, K.T., and Krol, W.F.: The "Constant Intake Rate Assumption in Interim Recruitment Goal Methodology for Multicenter Clinical Trials." Journal of Chronic Diseases, 40(4):297-307, 1987.

Bingham, S.F., Collins, J.F., Weiss, D.G., Williford, W.O., and Krol, W.F.: Significance: Clinical or Statistical? (Letter to Editor). Thrombosis and Haemostasis, 61:323-324, 1989.

Hobson, R.W., Song, I.S., George, A.M., and Weiss, D.G.: Results of arteriography for asymptomatic carotid stenosis. Stroke, 20(Abstract):135, 1989.

Towne, J.B., Weiss, D.G., Hobson, R.W.: First Phase Report of Cooperative VA Asymptomatic Stenosis Study - Operative Morbidity and Mortality. Journal of Vascular Surgery, 2:252, 1989.

Mayberg, M.R., Wilson, S.E., Yatsu, F., Weiss, D.G., et al.: Carotid Endarterectomy and Prevention of Cerebral Ischemia in Symptomatic Carotid Stenosis. Journal of the American Medical Association, 266:3289-94, 1991.

Hobson, R.W., Weiss, D.G., Fields, W.S., Goldstone, J., Moore, W.S., Towne, J.B., Wright, C.B., et al.: Efficacy of Carotid Endarterectomy for Asymptomatic Carotid Stenosis, New England Journal of Medicine, 328:221-227, 1993.

Krupski, W.C., Weiss, D.G., Rapp, J.H., Corson, J.D., Hobson, R.W., et al.: Adverse Effects of Aspirin in the Treatment of Asymptomatic Carotid Artery Stenosis: Complications Related to High and Low Dose Protocols. Journal of Vascular Surgery, 16:588-600, 1992.

Wilson, S.E., Mayberg, M.R., Yatsu, F., Weiss, D.G.: Crescendo TIAs: A Surgical Imperative. Journal of Vascular Surgery, 17:249-256, 1993.

## CURRICULUM VITA (Cont.)

DAVID G. WEISS, Ph.D.

### Publications (Cont.)

Hobson, R.W., Krupski, W.C., Weiss, D.G.: Influence of Aspirin in the Management of Asymptomatic Carotid Stenosis. Journal of Vascular Surgery, 17:257-265, 1993.

Cohen, S.N., Hobson, R.W., Weiss, D.W., Chemowitz, M.I.: Mortality Associated with Asymptomatic Carotid Stenosis: Long Term Clinical Evaluation. Submitted to Journal of Vascular Surgery, June 1993.

Srinivasan, J., Mayberg, M.R., Weiss, D.G., Eskridge, J., Yatsu, F., Wilson, S.E.: Duplex Accuracy Compared to Angiography in the Veterans Affairs Cooperative Studies Trial for Symptomatic Carotid Stenosis. Submitted to Stroke, July 1993.

Chimowitz, M.I., Weiss, D.G., Cohen, S.L., Starling, M.R., Hobson, R.W.: Cardiac Prognosis of Patients with Carotid Stenosis and No History of Coronary Artery Disease. Submitted to New England Journal of Medicine, June 1993.

### Presentations:

Wertz, R.T., Collins, M.J., Weiss, D.G., Brookshire, R.H., Friden, T., Kurtzke, J.F., Pierce, J.: VA Cooperative Study on Aphasia: Comparison of Individual and Group Treatment, Preliminary Report. Paper presented at AAAS meeting, Washington, DC, Feb., 1978.

Collins, J.F., Bingham, S.F., Weiss, D.G., Williford, W.O., Kuhn, R.: Patient Intake in VA Cooperative Studies. Paper presented at Sixth Annual Symposium on Coordinating Clinical Trials, Boston, MA, May, 1979.

Collins, J.F., Bingham, S.F., Williford, W.O., Weiss, D.G.: Who Drops Out of Clinical Trials - The VA Cooperative Study Experience. Paper presented at Society for Clinical Trials and Eighth Annual Symposium for Coordinating Clinical Trials, San Francisco, CA, May, 1981.

Collins, J.F., Williford, W.O., Bingham, S.F., Weiss, D.G., Klett, C.J.: Planning Patient Recruitment: Fantasy and Reality. Presentation at National Cancer Institute and National Heart, Lung and Blood Institute Workshop on Evaluation of Therapy, NIH, Bethesda, MD, September, 1983.

Weiss, D.G., Williford, W.O., Collins, J.F., Bingham, S.F.: Training of Biostatisticians for Clinical Trials: A Survey: Session on Teaching Statistics in Health Sciences: Training, Resources, and Practice; S.P. Azen, Ph.D., Chairman, ASA Annual Meeting, Toronto, Canada, August, 1983. (Invited Talk)

Morhart, R.E., Becker, M., Weiss, D.G.: Long Term Patient Compliance with Self-Care Control Methods. Paper presented at International Association of Dental Research meeting, New Orleans, March, 1984.

## CURRICULUM VITA (Cont.)

DAVID G. WEISS, Ph.D.

### Presentations (Cont.):

Wertz, R.T., Aten, J.L., Weiss, D.G., Brookshire, R.H., Garcia-Bunuel, L., Holland, A.H., LaPointe, L.L., Kurtzke, J.F., Milianti, F.J., Brannegan, R., Greenbaum, H., Marshall, R.C., Vogel, D., Carter, J.E., Barnes, N.S., Goodman, R.: VA Cooperative Study on Aphasia: Comparison of Clinic, Home, and Deferred Treatment. Paper presented at American Congress of Rehabilitation Medicine, Boston, MA, October 24, 1984; Academy of Aphasia, Los Angeles, CA, October 30, 1984.

### Other

**Experience:** Study Biostatistician for planning and/or analysis of the following VA Cooperative Studies:

- CS# 17 VA Cooperative Study on Aphasia: A Comparison of Individual and Group Therapy.
- CS# 59 Patient Compliance and its Role in Dental Plaque Control.
- CS# 85 Antabuse in the Treatment of Alcoholics on Methadone Maintenance.
- CS#110 A Comparison of Hospital and Home Treatment Programs for Aphasic Patients.
- CS#167 Asymptomatic Carotid Stenosis - Etiological Importance in Development of Stroke.
- CS#271 Long-Term Follow-Up of WW-II and Korean Conflict Prisoners-of-War.
- CS#292 Therapy of Primary Amyloidosis (AL).
- CS#309 The Role of Carotid Endarterectomy in Preventing Stroke from Symptomatic Carotid Stenosis.
- CS#328 The Molecular Genetics of Psychiatric Disorders.
- CS#352 Colchicine in the Treatment of Cirrhosis of the Liver
- CS#366 Psychiatric Genetic Linkage
- CS#380 Prospective Evaluation of Risk Factors for Large ( $\geq 1$  cm) Colonic Adenomas in Asymptomatic Subjects
- CS#391 Effect of Polyunsaturated Lecithin on Liver Fibrosis
- CS#407 Prostate Cancer Intervention Versus Observation Trial (PIVOT): A Randomized Trial Comparing Radical Prostatectomy Versus Palliative Expectant Management for the Treatment of Clinically Localized Prostate Cancer

**APPENDIX D**  
**NCI LETTER**





## MEMORANDUM

National Institutes of Health  
National Cancer Institute  
Bethesda, Maryland 20892

**To:** Timothy J. Wilt, MD, MPH

**From:** Richard S. Kaplan, MD, Senior Investigator, CIB, CTEP, NCI

**Date:** 29 July 1993

**Subject:** PIVOT (Prostate cancer Intervention Versus Observation Trial)

I wanted to summarize for you and for the Dept. of Veterans Affairs Cooperative Studies Program (CSP) the position of support of the Cancer Therapy Evaluation Program of NCI for the PIVOT trial, and how our Cooperative Clinical Trials Groups and other clinical investigators will participate.

First of all, let me reiterate that the scientific rationale for this protocol is viewed as having the highest possible priority to our clinical trials program in prostate cancer. The issues to be addressed in this study have profound implications for most of the other trials under way or planned for early stages of the disease, as well as having critical implications for public health and health care policy. Moreover, the publicity surrounding recent data presentations gives us a window of opportunity of which we need to take advantage to perform what is clearly a most challenging clinical trial.

The challenging part, of course, is to test the strong biases that have long determined patterns of referral and care for prostate cancer patients and this, coupled with the required scale of the trial is such that it would be impossible to mount in our Cooperative Groups alone since they depend substantially on accrual from academic and other referral practices. On the other hand, it might also not be feasible in the Department of Veteran Affairs either without substantial accrual assistance from the Cooperative Group system.

CTEP staff therefore have extensively discussed the protocol, and its importance, with the Group Chairmen and the GU or prostate chairs of all the adult Cooperative Groups and emphasized the priority that we are requesting for this trial within their strategic plans. We are also taking care that major Cooperative Group protocols that would compete for accrual with PIVOT will incorporate eligibility criteria or be prioritized such that eligible patients will be offered the PIVOT trial first.

The next steps for CTEP are to formalize commitment from one or several of our Groups and then to establish commitment of particular member institutions. I will be presenting the protocol in detail at the major Fall full meetings of SWOG, ECOG, NCCTG and CALGB, each of which has expressed substantial interest. From these resources, we anticipate identifying at least 30-40 centers (hopefully more) who will be major participants. We are currently figuring on enrolling about 8 patients per center per year (out of perhaps 50 /year eligible and screened) over 3 years of accrual at each non-DVA center.

Data management and statistical support will be from the DVA Cooperative Studies Program and

without cost to NCI, though it seems to us that the most efficient and reliable strategy would be to have the Groups collect the data in their own Ops/Stat Offices, using a format compatible with that of the DVA-CSP and then forward them. This plan will have the advantage of utilizing the established methods of data quality assurance. However, substantial work may need to be done to develop a common data format. As soon as the CTEP Groups are formally committed (via their committee structures) it will be critical to have personnel from their respective ops/stat offices meet with DVA-CSP staff to coordinate methods of data collection.

Which of course brings us to the question of costs. There will clearly be a need for some cost supplement to the Cooperative Group op/stat offices. For the participating Group members, a substantial portion of the costs will be offset according to their routine Group reimbursement formulas but there is no question that PIVOT will be a personnel-intensive undertaking with some special requirements, and the VA is apparently not in a position to supplement Group members for their participation. Since this trial is every bit as important to DCT as it is to the VA, CTEP is going to find funds to help make it possible for Group members to take on the additional costs of case-finding and what is expected to be a very time-consuming process of acquiring informed consent. We will also push to have PIVOT made an NCI-designated High Priority Trial, which will make additional funds available as well as augmenting its visibility.

Dr. Friedman is confident that CTEP can deliver the support necessary to assure enthusiastic participation in the PIVOT trial by a substantial proportion of its GU investigators and help to assure completion of this key study. He and I are also enthusiastic about the precedent for inter-agency clinical trials of major importance and impact.

cc: Dr. Friedman  
Dr. Ungerleider

**VA COOPERATIVE STUDY 407**  
**"PROSTATE CANCER INTERVENTION VERSUS OBSERVATION TRIAL (PIVOT):**  
**A RANDOMIZED TRIAL COMPARING RADICAL PROSTATECTOMY VERSUS**  
**PALLIATIVE EXPECTANT MANAGEMENT FOR THE TREATMENT OF**  
**CLINICALLY LOCALIZED PROSTATE CANCER"**

**VOLUME II**  
**SUPPORTING INFORMATION**

**- PRIVILEGED AND CONFIDENTIAL -**

Not to be Disseminated Beyond its Official

Committee Function and Use

August, 1993



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VOLUME II

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**APPENDIX E**  
**BIostatistical AND RESEARCH DATA PROCESSING**  
**(BRDP)**



## **BIOSTATISTICAL AND RESEARCH DATA PROCESSING (BRDP)**

### **I. DATA MANAGEMENT**

This study will be a prospective, randomized trial of two therapeutic management approaches for localized cancer of the prostate (CAP). The two treatments approaches are radical prostatectomy (RP) with aggressive follow-up treatment and expectant management (EM) with palliative symptomatic treatment only. Patients meeting the general inclusions/exclusion criteria for the study will be randomized (by telephone call to the CSPCC at Perry Point) to one of the two management approaches and followed until death or the completion of study follow-up. The trial is planned for 15 years which includes a three-year intake period and a 12-year follow-up beyond the last randomization. Data to be collected at entry includes: patient profile (age, race, family history of CAP activities of daily living (ADL); health status questionnaire with prostatic specific items; complete medical history (with Charlson Score); and, clinical staging information (T,N,M stage, size by DRE, Gleason grade, and histologic grade). For patients assigned to the radical prostatectomy arm, surgical information will be recorded that includes pelvic lymph node dissection, descriptive characteristics of the prostatectomy procedures, pathologic staging, and surgical complications. Follow-up visits will be scheduled for all patients at six weeks (one month postop for surgical group), 3, 6, 9, 12 months and every 6 months thereafter until completion of the study. Data to be collected at routine follow-up visits includes: symptom report; pain report; ADL report; bone scan (annually); CAP status and treatment report; clinical staging; tumor size by DRE; and, the quality-of-life/health status questionnaire (annually). In addition, all episodes of CAP treatment will be reported as it is provided on a special treatment summary form. Two lab measures, PSA and PAP, will be evaluated centrally to monitor for safety and results will be reported directly to the CSPCC. Neither PSA nor PAP results will be returned to the sites. Biopsy samples from the RP group will be submitted for central review and histopathologic staging and grading. Complete documentation will be required on each death including a narrative summary from the Participating Investigator, hospital discharge summary with clinical chart, autopsy report and/or copy of death certificate. This documentation will be blinded for treatment group and submitted to the Endpoint Committee for adjudication.

At each participating site, data collection will be carried out under the direction of the PI. Data will be recorded on specially developed study data forms (see Volume II, Study Forms). The final responsibility for the completeness and accuracy of all study data at a study center belongs to the Participating Investigator who will review all study forms and affix his signature to each form prior to submitting the forms to the CSPCC (Perry Point). Study forms will be printed on three-part NCR (noncarbon reproducing) paper. The original or top sheet will be submitted to the CSPCC, while the second sheet will be submitted to the Study Chairman's office. The only exception to this will be the informed consent documents where the originals will be kept at the participating center and copies submitted to the CSPCC and Study Chairman's office. A special data form has been developed for the lab studies (PSA, PAP) that will be completed centrally. The CSPCC will be sent the top sheet with the second sent to the Study Chairman's office and the bottom copy retained at the central lab. Results of these tests will not be returned to the local study center, but will be sent directly to the Study Chairman's office and the CSPCC. Separate from the study forms, each study patient death will be reported to the Study Chairman's office (with copies to the CSPCC) by the Participating Investigator in a narrative summary detailing the circumstances including cause, autopsy reports, copies of patient's chart, etc.

Study data forms received at the CSPCC will be processed at regular intervals (monthly). Data processing will consist of keyentering and keyverifying by study assistants directly into the computer. All data will be extensively computer edited with specially developed editing programs for the purpose of identifying errors such as missing data, values which are outside range limits, and consistency checks prior to entering the study master file. Possible data errors so identified by the edits will be listed on a computer printout and returned to the participating centers for correction and/or confirmation and resubmission to the CSPCC. Overall data flow will be monitored by the Study Biostatistician with special computer software that will summarize missing or delinquent forms as well as provide different measures of data accuracy. Monitoring will also include random checks comparing values in the study masterfile with those on the corresponding data form.

The data flow system described above will result in an updated study masterfile being available at any point in time. Periodic reports will be prepared and provided to the Study Group, Executive Committee, and Data Monitoring Board while the study is ongoing. These are currently planned for approximately six-month intervals to coincide with the annual study meetings and with



additional monitoring reports in between (current meeting schedule: start-up, nine months, annually thereafter). The content of these reports will be described in the sections to follow. A diagram of the data flow for this study appears in Figure 1.

## **II. INTERIM MONITORING REPORTS TO THE STUDY EXECUTIVE COMMITTEE**

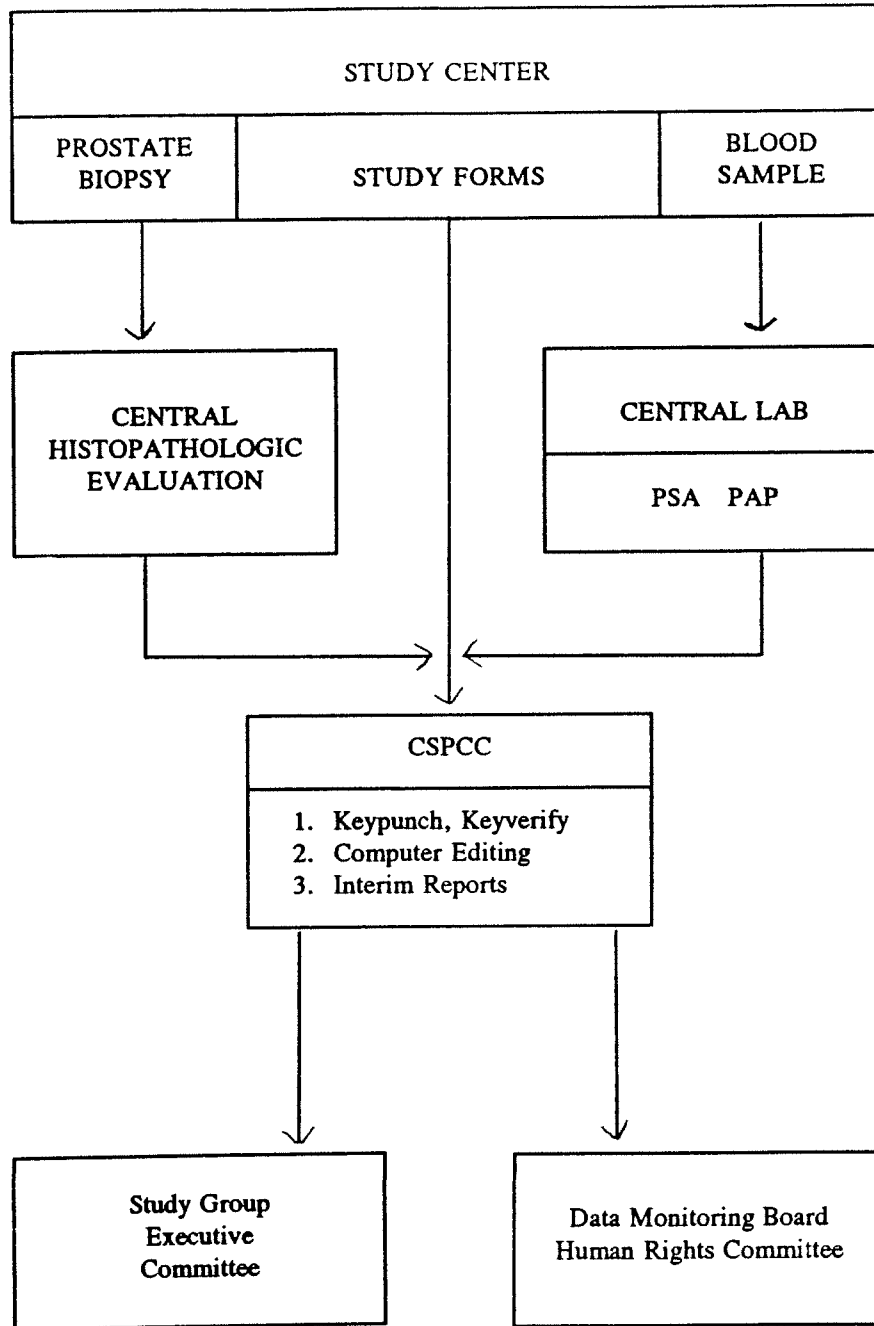
### **A. Patient Screening and Enrollment**

During the patient enrollment period, it will be necessary to monitor whether or not enrollment targets are being met. Patient screening information will be recorded on Form 1 which provides a check list of the study inclusion/exclusion criteria. The screening data summaries will be presented in a number of different formats. The monthly screening record will be presented as in Table 1 (example tables appear on pages 99-106). This table will provide both separately, for each month, and cumulatively the numbers of patients screened and rejected along with associated percentages for rejection rates and enrollment rates with respect to projected targets. Table 1 will be provided for all centers combined and separately for each center. The cumulative number of patients enrolled as a percentage of expected will be provided graphically as in Figure 2. Cumulative screening summaries for all patients will be listed by study center as in Table 2. In order to evaluate which screening criteria most affect patient intake, a summary of the reasons for exclusion will be provided as in Table 3, for all centers combined.

### **B. Study Patient Characteristics at Entry**

The Executive Committee and Study Group report will include descriptive statistical summaries characterizing study patients at entry. Background information will be recorded on study Form 2 and includes demographic measures such as age, race, family history of CAP, performance status, smoking history, medical history (Charlson Score), laboratory data and clinical staging. Race, performance status, family history, medical history and clinical staging will be recorded as categorical variables while age, and laboratory data will be recorded as continuous response variables. Descriptive summaries for categorical variables will be frequencies with percentages and treatment groups will be compared by chi-square procedures; continuous variables will be summarized by means and standard deviations and treatment group comparisons will be by analysis of variance. Background data summaries will be presented as in Table 4 where age (continuous) and

FIGURE 1  
DATA FLOW



race (categorical) appear as examples. In addition, laboratory data for each variable will be classified as abnormal/normal and will be summarized as a categorical variable with frequency of abnormal values appearing similar to race in Table 4.

At the time of entry, biopsy material from patients in the surgical group (RP) will be evaluated by the central histology lab. The evaluation will be performed and the results will be recorded on Form 8. Histologic grading will determine the degree of differentiation that can be determined for the tumor. This histologic grade will be summarized as in Table 5. In addition, patients undergoing radical prostatectomy will have descriptive information (including complications) about the procedures recorded (Form 3) as well as pathologic staging by the TNM system. This information is generally recorded as categorical responses and will be summarized as in Table 6 where type of procedure appears as an example.

All patients will be asked to fill out a health status questionnaire at entry and annually thereafter. This questionnaire incorporates the SF-36 Health Status Survey and augments it with the AUA Symptom Index, a Bothersome Index, prostate specific questions (uro-sexual functioning), and items of overall health. These measures consist primarily of rating scales as responses. Individual items will be summarized both by frequency and percent as well as mean rating scores and treatment groups compared by analysis of variance. An example, bodily pain, appears as in Table 7. Composite scores for similar items will be presented with means and standard deviations (as in Table 7) and compared by analysis of variance.

The baseline summaries as described above will permit the monitoring of treatment groups with respect to possible imbalances that may occur in important prognostic variables. Variables so identified will be possible candidates for statistical adjustment procedures at the time of final analysis. The randomization process, in general, works adequately with respect to baseline distributions; nonetheless, the monitoring as outlined in this section will provide an ongoing confirmation of treatment group balance.

### C. Data Quality Reports

The Executive Committee and Study Group will also receive information on selected measures of data quality. This will consist primarily of measures of missing data. In order that the study reach a successful conclusion, the amount of missing data must be minimized with continual efforts directed at reducing rates of missing data to zero. The number of missing forms will be presented as in Table 8 where regularly scheduled forms are listed by form. The percent of missing forms will be based on the expected number due at a given date. These data will provide a general assessment of whether or not centers are following patients adequately as defined by the study protocol and whether corrective action may be indicated. A second type of missing data information that will be presented is missing items per form. These will be given as in Table 9, where the number of missing items per form is presented. As part of the computer editing system, participating centers will receive periodic reports indicating missing values and/or values outside acceptable limits which will then have to be provided or corrected as necessary. An ongoing review by the Executive Committee will serve the purpose of identifying early on any problem areas with the forms or participating centers with respect to data quality.

### **III. MONITORING REPORT TO THE DATA MONITORING BOARD**

The function of the Data Monitoring Board is to serve as the outside or independent review committee that oversees all aspects of the study while ongoing. It includes individuals with demonstrated expertise in the research questions addressed by the study, but who have no role in planning or conducting the study. This committee is empowered to terminate the study if sufficient evidence accumulates to question the general feasibility of continuing. The interim report to this committee will include all the information provided to the Executive Committee as described earlier. In addition, the committee will receive data summaries of accumulating outcome data at regular intervals. The analyses that will be included will be described in the next section on final analysis and will constitute reports of preliminary results.

#### **IV. FINAL ANALYSIS**

##### **A. Study Patient Characteristics at Enrollment**

This section of the report to the Data Monitoring Board will provide descriptive summaries of study patient characteristics at entry into the study. Included will be background and medical history with laboratory results, histologic grading, health status/quality of life. These measures have been reviewed in detail in the previous section of this appendix which discussed the Study Group and Executive Committee Report. The Data Monitoring Board will receive the same material in an ongoing way as it accumulates. The final analysis of these data will include all the analyses as described earlier but on the final and complete data set.

##### **B. Study Follow-up**

Patients enrolled in the study will be followed from the time of randomization until death or completion of the 15-year study period. Routine follow-up visits are scheduled at 6 weeks (one month postop for the RP group), 3, 6, 9, 12 months, and every 6 months thereafter. Data collection during the extensive follow-up period by design will be limited to that which is essential for monitoring the course of prostate cancer. It will include: urologic symptoms and pain assessment, performance status (activities of daily living), annual bone scan, clinical status, tumor staging and size (by DRE) (Form 4); complete documentation of each course of treatment provided for CAP (Form 5); quality of life/health status with urologic symptoms and sexual function (Form 6); and, routine blood monitoring for PSA and PAP by central lab evaluation (Form 9). The clinical status items listed above (Form 4) are recorded as categorical data and will be summarized and presented as in Table 10 where bone pain appears as an example. Treatment group comparisons will be by chi-square procedures. Data summaries will include frequencies by rating period along with change from previous rating periods. The format of Table 10 will also be adopted in presenting PSA and PAP measures (Form 9) which will be classified according to threshold values both for frequencies at each rating period and to characterize change between rating periods. Each time a patient undergoes treatment for CAP, the details will be appropriately recorded (Form 5). These will include the reasons (local, regional, metastatic disease), type (mechanical, surgical, radiation, brachy, or systemic), and response to treatment. This information is recorded as categorical data and summaries will be presented as in Table 11 where

pelvic pain and chemotherapy appear as examples of reason and type of treatment. Comparisons will be by chi-square tests. Patients will be administered the health status questionnaire (Form 6) annually in order to assess quality of life and self perceptions of degree of disability. As noted in an earlier section, the health status questionnaire assesses general and prostate specific aspects of health and daily functioning by employing series of questions for which the responses typically are standard rating scales. Data summaries will be based on composite scores for the different components of the questionnaire that are formed by totaling the appropriate response items. For example, urologic symptoms will be assessed by the AUA (American Urologic Association) Symptom Index comprised of seven questions, each with a six-point rating (0=Not at all, 5=Almost Always) as a response. A total score will be derived and presented as in Table 12. A two-way repeated measures analysis of covariance will be performed in order to compare treatment groups and to evaluate the scores for their response profiles over time.

### C. Mortality

The primary outcome measure for this study is all-cause mortality. The primary statistical analysis will compare the two treatment approaches, radical prostatectomy and expectant management, on the basis of time until death as measured from the date of randomization. Survival curves will be estimated with Kaplan-Meier methodology and will be compared by the logrank statistic.

In addition to all-cause mortality, a secondary objective will be to compare the two management approaches on the basis of prostate cancer specific mortality. Each death will be documented as extensively as possible including autopsy reports, patient chart and narrative summary provided by the PI. Documentation (blinded to treatment group) will be submitted to the Endpoint Committee for final classification as to whether or not the death was prostate cancer related. The same procedure used to evaluate all-cause mortality will then be applied to prostate cancer specific mortality.

In summary, this study has been planned to evaluate two treatment management approaches for localized prostate cancer. Ongoing analyses for the purpose of monitoring as well as final analysis have been described in this Appendix BRDP. This study will be viewed by the medical community as the major definite clinical trial that will determine whether or not radical prostatectomy will be used in the future in treating localized cancer of the prostate.

TABLE 1  
MONTHLY SCREENING RECORD

MONTH	NUMBER OF PATIENTS			CUMULATIVE NUMBER				
	SCREENED	REJECTED	ENR	SCREENED	REJECTED	ENR	% ENR/EXP	% REJECTED
1								
2								
3								
.								
.								
.								
36								

FIGURE 2

NUMBER OF PATIENTS ENROLLED IN TREATMENT STUDY  
AS PERCENT OF EXPECTED: CUMULATIVE MONTHLY RATES

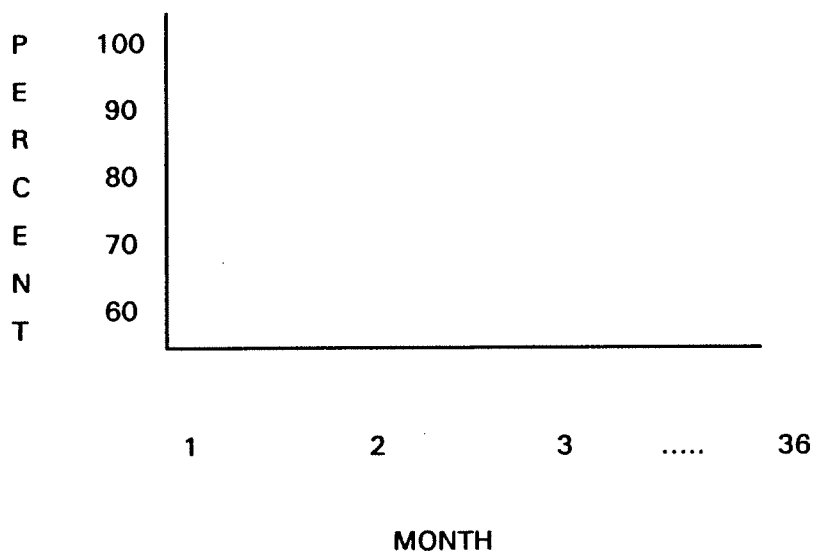


TABLE 2  
CUMULATIVE SCREENING SUMMARY: ALL PATIENTS, BY CENTER

STUDY CENTER	TOTAL NUMBER OF PATIENTS				
	<u>SCREENED</u>	<u>REJECTED</u>	<u>ENROLLED</u>	<u>% OF EXPECTED</u>	<u>% REJECTED</u>
1					
2					
3					
.					
.					
.					
TOTAL					



**TABLE 3**  
**SUMMARY OF INELIGIBILITY: REASONS FOR EXCLUSION,**  
**ALL CENTERS**

REASON	SCREENED	REJECTED:	% of SCR	# Rejected as Only Reason	% of SCR
AGE					
PSA > 100					
BONE SCAN					
NONLOCALIZED CAP					
.					
.					
.					
REFUSAL TOTAL					

**TABLE 4**  
**BACKGROUND HISTORY AT ENTRY**

	RP	EM	P VAL
MEAN AGE (SD)			
RACE			
AMERICAN INDIAN			
ASIAN/PACIFIC ISLANDER			
BLACK/NOT HISPANIC			
WHITE/NOT HISPANIC			
OTHER			
TOTAL			

TABLE 5

CENTRAL HISTOLOGIC EVALUATION AT ENTRY:  
RADICAL PROSTATECTOMY PATIENTS

	#	%
NUMBER OF PATIENTS		
HISTOLOGIC GRADE		
WELL DIFFERENTIATED		
MODERATELY DIFFERENTIATED		
POORLY		
DIFFERENTIATED/UNDIFFERENTIATED		
UNKNOWN		
TOTAL		

TABLE 6

SUMMARY OF RADICAL PROSTATECTOMY PROCEDURE

	#	%
NUMBER OF PATIENTS		
TYPE OF PROCEDURE		
NERVE SPARING - UNILATERAL		
NERVE SPARING - BILATERAL		
NONNERVE SPARING		

TABLE 7  
HEALTH STATUS QUESTIONNAIRE

INDIVIDUAL ITEM	RP		EM		P VAL
	#	%	#	%	
BODILY PAIN/LAST 4 WEEKS					
NONE					
VERY MILD					
MILD					
MODERATE					
SEVERE					
VERY SEVERE					
TOTAL					
MEAN					
S.D.					

TABLE 8  
NUMBER AND PERCENT OF MISSING FORMS: BY CENTER

	<u>CENTER 1</u>		<u>CENTER 2</u>		...	<u>CENTER N</u>		<u>TOTAL</u>	
	#	%	#	%		#	%	#	%
FORM									
INFORMED CONSENT									
FORM 1 Screening									
FORM 2 Background Information									
.									
.									
.									

TABLE 9  
NUMBER AND PERCENT OF FORMS WITH MISSING ITEMS: BY CENTER AND FORM

	<u>CENTER 1</u>		<u>CENTER 2</u>		...	<u>CENTER N</u>		<u>TOTAL</u>	
	#	%	#	%		#	%	#	%
FORM 1									
SCREENING									
.									
.									
.									

TABLE 10  
 CLINICAL STATUS DURING FOLLOW-UP: BONE PAIN

BONE PAIN	SINCE LAST VISIT												
	NEW PAIN						PAIN GONE						
	RP		EM		RP		EM		RP		EM		
MONTH	N	#	%	N	#	%	P-VALUE	N	#	%	N	#	%
6 (WEEK)													
3													
6													
9													
12													
18													
.													
.													
.													

TABLE 11  
TREATMENT FOR CANCER OF PROSTATE

REASON	RP		EM		P-VALUE
	# PATS	%	# PATS	%	
PELVIC PAIN					
TYPE					
CHEMOTHERAPY:					
RESPONSE					
CR					
PR					
PROG DZ					
UNK					

TABLE 12

HEALTH STATUS QUESTIONNAIRE

	RP			EM		
	N	MEAN	S.D.	N	MEAN	S.D.
AUA SYMPTOM INDEX						
MONTH PRE						
6 WEEK						
3						
6						
9						
12						
.						
.						
.						

**APPENDIX F**  
**STUDY FORMS**





## **CSP #407 STUDY FORMS**

### **SCREENING LOG**

<b>FORM 01</b>	<b>SCREENING</b>
<b>FORM 02</b>	<b>BACKGROUND INFORMATION</b>
<b>FORM 03</b>	<b>SURGICAL</b>
<b>FORM 04</b>	<b>CLINIC VISIT FOLLOW-UP</b>
<b>FORM 05</b>	<b>SUMMARY OF TREATMENT FOR CAP</b>
<b>FORM 06</b>	<b>HEALTH STATUS QUESTIONNAIRE</b>
<b>FORM 07</b>	<b>TERMINATION</b>
<b>FORM 08</b>	<b>CENTRAL HISTOPATHOLOGIC</b>
<b>FORM 09</b>	<b>CENTRAL BLOOD LABORATORY</b>



Medical Center Name \_\_\_\_\_ Medical Center No. \_\_\_\_\_

INSTRUCTIONS: All patients with a new diagnosis of prostate cancer should be included on this log. Mail to the Coordinating Center when all lines on a page are completed.

Screening Number	Name	Social Security No.	Age	Race <sup>1</sup>	Date of Biopsy (Mo/Day/Yr)	Gleason Grade <sup>2</sup>	Histologic Grade <sup>3</sup>	PSA (ng/ml)	Bone Scan? 1 = Positive 2 = Negative 3 = Not Done 9 = Unknown	Was screening visit scheduled? 1 = Yes 2 = No
9001	_____	_____	_____	_____	_____	_____	_____	_____	_____	_____
9002	_____	_____	_____	_____	_____	_____	_____	_____	_____	_____
9003	_____	_____	_____	_____	_____	_____	_____	_____	_____	_____
9004	_____	_____	_____	_____	_____	_____	_____	_____	_____	_____
9005	_____	_____	_____	_____	_____	_____	_____	_____	_____	_____
9006	_____	_____	_____	_____	_____	_____	_____	_____	_____	_____
9007	_____	_____	_____	_____	_____	_____	_____	_____	_____	_____
9008	_____	_____	_____	_____	_____	_____	_____	_____	_____	_____
9009	_____	_____	_____	_____	_____	_____	_____	_____	_____	_____
9010	_____	_____	_____	_____	_____	_____	_____	_____	_____	_____
9011	_____	_____	_____	_____	_____	_____	_____	_____	_____	_____
9012	_____	_____	_____	_____	_____	_____	_____	_____	_____	_____
9013	_____	_____	_____	_____	_____	_____	_____	_____	_____	_____
9014	_____	_____	_____	_____	_____	_____	_____	_____	_____	_____

<sup>1</sup> Race

- 1 = American Indian or Alaskan Native
- 2 = Asian or Pacific Islander
- 3 = Black, not of Hispanic origin
- 4 = Hispanic
- 5 = White, not of Hispanic origin
- 6 = Other, specify \_\_\_\_\_

<sup>2</sup> Gleason Grade:

- Gleason Score 1 (1-5)
- Gleason Score 2 (1-5)
- Gleason Sum (Grade) (2-10; 98 = Unsatisfactory; 99 = No grade possible)

<sup>3</sup> Histologic Grade:

- 1 = Well differentiated
- 2 = Moderately well differentiated
- 3 = Poorly differentiated/Undifferentiated
- 9 = Unknown

(Exclusion Criteria: Age > 75; nonlocalized CAP; diagnosis of CAP > 6 months ago; PSA > 100; positive bone scan; life expectancy < 10 years; prior therapy for CAP other than TURP)

Screening No.

S.S.#  -  -

Patient Name \_\_\_\_\_

Patient No.

Medical Center No.

Medical Center Name \_\_\_\_\_

Date Completed Mo  Day  Yr

**INSTRUCTIONS: THIS FORM SHOULD BE COMPLETED ON ALL PATIENTS WITH A DIAGNOSIS OF PROSTATE CANCER WHO WERE SCREENED FOR ENTRY INTO THIS STUDY.**

1= YES  
2= NO  
3= NS\*

**A. EXCLUSION CRITERIA (\*NS=Not Screened)**

- 1. Age more than 75 years .....
- 2. PSA > 100 ng/ml .....
- 3. Bone scan consistent with metastatic disease .....
- 4. Other imaging or laboratory studies indicating that prostate cancer is nonlocalized .....
- 5. Other evidence that cancer of the prostate is not clinically localized .....
- 6. Diagnosis of prostate cancer greater than 6 months ago .....
- 7. Significant coexisting medical conditions or high surgical risks:
  - A. Life expectancy less than 10 years .....
  - B. Serum creatinine greater than 3 mg/dl .....
  - C. Myocardial infarction within last 6 months .....
  - D. Unstable angina .....
  - E. New York Heart Association Class III or IV congestive heart failure .....
  - F. Severe pulmonary disease .....
  - G. Liver failure .....
  - H. Severe dementia .....
  - I. Debilitating illness .....
  - J. Other malignancies except skin cancer .....
- 8. Prior therapy for CAP (pelvic irradiation, chemotherapy, anti-androgen or androgen deprivation therapy except 5-alpha reductase inhibitors [Proscar]) .....
- 9. Prostate surgery other than TURP .....
- 10. Current use of estrogens or androgen blocking drugs .....
- 11. Uncooperative or unreliable patient .....
- 12. Participating in another interventional study .....

Medical Center No.

Screening No.

Patient No.

**B. INFORMED CONSENT**

13. Did patient view the informational video? (1=Yes, 2=No) .....

14. Did patient sign consent form for participation in the study? (1=Yes, 2=No) .....

**IF PATIENT SIGNED THE INFORMED CONSENT, GO TO SECTION C.**

If the patient refuses to sign informed consent, which of the following reasons was the major reason for refusal and which were contributing, but not major problems.

**1=Not a factor  
2=Major factor  
3=Contributing,  
but not major**

15. Patient not willing to participate in research of any kind .....

16. Patient not willing to receive "experimental" form of therapy .....

17. Patient fears participating will interfere with receiving proper treatment .....

18. Patient not willing to leave decision for treatment to chance .....

19. Patient prefers treatment elsewhere .....

20. Patient declines for other reason .....

Specify \_\_\_\_\_

21. Physician prefers that patient not participate .....

22. Others (family, etc.) prefer that patient not participate .....

**C. RANDOMIZATION**

23. Patient's randomization status (1=Ineligible, 2=In study) .....

**IF IN STUDY:**

24. Date randomized ..... Mo   Day   Yr

25. Patient's randomization number (Patient No.) .....

**PLEASE ENTER PATIENT NO. ON TOP OF BOTH PAGES OF THIS FORM.**

P.I.'s Signature \_\_\_\_\_

Patient Name \_\_\_\_\_

Patient No.

Medical Center No.

Medical Center Name \_\_\_\_\_

Date Completed Mo

Day

Yr

**A. PATIENT PROFILE**

1. Date of birth ..... Mo  Day  Yr

2. Race .....

- 1=American Indian or Alaskan Native
- 2=Asian or Pacific Islander
- 3=Black, not of Hispanic origin
- 4=Hispanic
- 5=White, not of Hispanic origin
- 6=Other, specify \_\_\_\_\_

3. Family history of CAP? (1=Yes, 2=No) .....

4. What led to the prostate tissue sampling? .....

- 1=Bladder outlet obstructive symptoms
- 2=Other symptoms
- 3=Abnormal digital rectal exam
- 4=Abnormal TRUS
- 5=Elevated PSA
- 6=Change in PSA

**B. PERFORMANCE STATUS**

5. Please describe the patient's activities of daily living .....

- 0=Fully active
- 1=Symptoms but ambulatory and able to do light work
- 2=No work but self care and active 50% of waking hours
- 3=Limited self care, confined to bed or chair > 50% of waking hours
- 4=Completely disabled

**C. SMOKING HISTORY**

6. Has patient smoked >100 cigarettes in his life? (1=Yes, 2=No) .....

IF YES:

A. Years smoked on a regular basis .....

B. Current smoker? (1=Yes, 2=No) .....

1. If No, how many years ago did patient quit? .....

**D. CHARLSON SCORE**

1=YES  
2=NO

7. Has patient ever had a myocardial infarction? .....

8. History of chronic congestive heart failure? .....

9. History or current evidence of peripheral vascular disease? .....

10. History or current evidence of cerebrovascular disease? .....

11. Has patient ever had a stroke? .....

12. History of diabetes? .....

A. If Yes, end organ damage? .....

- D. CHARLSON SCORE (Cont.)** 1=YES  
2=NO
- 13. History or current evidence of dementia? .....
  - 14. History or current evidence of chronic pulmonary disease? .....
  - 15. History or current evidence of connective tissue disease? .....
  - 16. History or current evidence of peptic ulcer disease? .....
  - 17. History or current evidence of mild liver disease? .....
  - 18. History or current evidence of moderate or severe liver disease? .....
  - 19. History or current evidence of moderate or severe renal disease? .....
  - 20. History of cancer (other than skin, prostate, or invasive bladder cancer)? ..... 
    - A. If Yes, type of tumor (1=Leukemia, 2=Lymphoma, 3=Metastatic solid tumor, 4=Any other) .....
  - 21. History or current evidence of AIDS or ARC? .....

- E. OTHER MEDICAL HISTORY** 1=YES  
2=NO
- 22. Has patient had treatment for BPH? ..... 

IF YES, indicate treatments:

    - A. Watchful waiting .....
    - B. Alpha blocker .....
    - C. 5-alpha-reductase .....
    - D. TURP .....
    - E. Open simple prostatectomy .....
    - F. Other surgical, specify \_\_\_\_\_ .....
  - 23. Has the patient had a vasectomy? .....

- F. LABORATORY DATA**
- 24. PSA (ng/ml) .....    . 
    - A. PSA method (1=Abbot, 2=Hybritech) .....
  - 25. Bone Scan ..... 
    - 1=Normal
    - 2=Abnormal not suggestive of malignancy
    - 3=Abnormal, suggestive of malignancy
    - 4=Definitely malignant
  - 26. Creatinine (mg/dl) .....   .
  - 27. Hemoglobin (gm/dl) .....   .
  - 28. Platelet count (x 1000/ $\mu$ l) .....
  - 29. SGOT (AST) (U/L) .....
  - 30. Prothrombin time (seconds) .....   .

**G. CLINICAL STAGING INFORMATION**

31. Clinical stage of disease .....

- T
- X
- 0
- 1a (A1)
- 1b (A2)
- 1c
- 2a (B1)
- 2b (B2)

32. Tumor size (digital rectal exam) .....

1 = Not palpable  
 2 = Palpable but tumor  $\leq$  1.5 cm in greatest dimension  
 3 = > 1.5 cm in greatest dimension  
 4 = Not stated/unknown

33. Gleason Grade .....

(Gleason Score 1 [1-5]; Gleason Score 2 [1-5]; Gleason Sum [Grade] 2-10; 98 = Unsatisfactory; 99 = No grade possible)

34. Histologic Grade .....

1 = Well differentiated  
 2 = Moderately well differentiated  
 3 = Poorly differentiated/Undifferentiated  
 9 = Unknown

35. Were any of the following imaging/laboratory studies used to confirm that CAP was clinically localized: 1 = YES  
2 = NO

A. PAP .....

B. TRUS .....

C. CT .....

D. MRI .....

E. Other, specify \_\_\_\_\_

36. BLOOD SENT TO CENTRAL LAB? .....

P.I.'s Signature \_\_\_\_\_



Patient Name \_\_\_\_\_ Patient No.  Medical Center No.

Medical Center Name \_\_\_\_\_ Date Completed Mo  Day  Yr

**INSTRUCTIONS: COMPLETE THIS FORM AND SUBMIT WITHIN 30 DAYS OF SURGERY. RECORD ANY SURGICAL COMPLICATIONS THAT OCCUR WITHIN 30 DAYS OF SURGERY OR PRIOR TO DISCHARGE ON PAGE 3 OF THIS FORM.**

**A. BIOPSY OR FINE NEEDLE ASPIRATION (FNA)**

1. Date of original diagnostic biopsy/FNA ..... Mo  Day  Yr

A. Biopsy/FNA sent to Central Lab? (1=Yes, 2=No) .....

**B. PELVIC LYMPH NODE DISSECTION**

2. Was the pelvic lymph node dissection done? (1=Yes, 2=No, 3=Unknown) .....

A. If NO, why not? \_\_\_\_\_

If YES, complete the following:

B. Date of pelvic lymph node dissection ..... Mo  Day  Yr

C. Number of days since registration .....

D. Pathologic nodal status (1=Negative, 2=Positive, 3=Unknown) .....

E. Were the nodes resectable? (1=Yes, 2=No, 3=Unknown) .....

F. Were the external iliac nodes dissected? (1=Yes, 2=No, 3=Unknown) .....

G. Were the hypogastric obturator nodes dissected? (1=Yes, 2=No, 3=Unknown) .....

**C. PROSTATECTOMY**

3. Was the prostatectomy done? (1=Yes, 2=No, 3=Unknown) .....

If NO, complete the following:

A. Indicate reason .....

- 1=Patient refusal
- 2=MD recommendation
- 3=Alternative therapy for prostate cancer
- 4=New diagnosis of high surgical risk
- 5=Other, specify \_\_\_\_\_

B. Describe reason for no surgery: \_\_\_\_\_  
\_\_\_\_\_

If YES, complete the following:

C. Date of prostatectomy ..... Mo  Day  Yr

D. Number of days since pelvic lymph node dissection .....

E. Type of surgical approach (1=Retropubic, 2=Perineal) .....

F. Type of procedure .....   
 1=Nerve-sparing unilateral  
 2=Nerve-sparing bilateral  
 3=Non-nerve-sparing

G. Was the prostate removed? (1=Yes, 2=No, 3=Unknown) .....

H. Were the seminal vesicles and ampulla of the Vater removed? (1=Yes, 2=No, 3=Unknown) .....

I. Was prostatectomy done on an Expectant Management patient? (1=Yes, 2=No) .....

4. Was prostatectomy delayed/cancelled? (1=Yes, 2=No, 3=Unknown) .....

A. If YES, indicate reason .....   
 1=Patient/personal reasons  
 2=Intercurrent clinical event  
 3=Physician recommended delay/cancellation  
 4=Study related  
 5=Other, specify \_\_\_\_\_

B. Describe reason for delay/cancellation: \_\_\_\_\_  
 \_\_\_\_\_

5. Pathologic stage of disease ..... T =   N =  M =

<u>T</u>	<u>N</u>	<u>M</u>
X	X	X
0	0	0
1a (A1)	1 (D1)	1a (D2)
1b (A2)	2 (D1)	1b (D2)
1c	3	1c (D2)
2a (B1)		
2b (B2)		
3a (C1)		
3b (C1)		
3c (C1)		
4a (C2)		
4b (C2)		

6. Pathologic extent of disease .....

- |                                       |                             |
|---------------------------------------|-----------------------------|
| 1=Radical prostatectomy not performed | 5=Surgical margins involved |
| 2=Confined to prostate                | 6=Seminal vesicle invasion  |
| 3=Capsular invasion                   | 7=Unknown                   |
| 4=Capsular penetration                |                             |

A. If "1" above, was metastatic site biopsied? (1=Yes, 2=No) .....

**D. SURGICAL COMPLICATIONS**

7. Did any surgical complications occur within 30 days of surgery? (1=Yes, 2=No) .....

If YES, complete the following:

	1=Yes 2=No		1=Yes 2=No
<i>Infections requiring antibiotics:</i>			
A. Pneumonia	<input type="checkbox"/>	J. Postoperative bleeding requiring transfusion	<input type="checkbox"/>
B. Wound infection	<input type="checkbox"/>	K. MI by enzymes or ECG	<input type="checkbox"/>
C. Urinary tract infection	<input type="checkbox"/>	L. Bowel injury requiring surgical repair	<input type="checkbox"/>
D. Sepsis	<input type="checkbox"/>	M. Catheter device present > 30 days post-op	<input type="checkbox"/>
E. Bacteremia	<input type="checkbox"/>	N. Death	<input type="checkbox"/>
F. Deep vein thrombosis	<input type="checkbox"/>	O. Additional surgical repair,	<input type="checkbox"/>
G. Stroke	<input type="checkbox"/>	specify _____	
H. Pulmonary embolus	<input type="checkbox"/>	P. Other,	<input type="checkbox"/>
I. Renal failure requiring dialysis	<input type="checkbox"/>	specify _____	

P.I.'s Signature \_\_\_\_\_

Patient Name \_\_\_\_\_ Patient No.  Medical Center No.

Medical Center Name \_\_\_\_\_ Date Completed Mo  Day  Yr

ENTER APPROPRIATE VISIT NUMBER FROM CODES ON BACK OF FORM .....

1. Did patient come in for clinic visit? (1=Yes, 2=No) .....

If YES:

A. Date of visit ..... Mo  Day  Yr

B. Was this a regularly scheduled protocol visit? (1=Yes, 2=No) .....

2. Since last visit, has patient had any of the following:

1=YES  
2=NO

A. Blood in urine .....

B. Swelling in legs .....

C. Change in bowel movements .....

PAIN:

D. Bone .....

E. Pelvic .....

F. If "Yes" to any of the above (A-E), were symptoms due to CAP .....

PERFORMANCE STATUS

3. Please describe the patient's activities of daily living since last visit .....

- 0=Fully active
- 1=Symptoms but ambulatory and able to do light work
- 2=No work but self care and active 50% of waking hours
- 3=Limited self care, confined to bed or chair > 50% of waking hours
- 4=Completely disabled

LABORATORY TEST - TO BE DONE ANNUALLY.

4. Bone scan .....

- 1=Normal
- 2=Abnormal, not suggestive of malignancy
- 3=Abnormal, suggestive of malignancy
- 4=Definitely malignant

5. Date of bone scan ..... Mo  Day  Yr

FOLLOW-UP TREATMENT/HOSPITALIZATION FOR CAP

6. Did patient receive treatment for CAP since last visit? (1=Yes, 2=No) .....   
 (If Yes, complete Form 05, Summary of Treatment for CAP.)
7. Compared to last visit, how would you describe the patient's clinical status with regard to CAP? .....   
 1=Clinically stable, no evidence of disease  
 2=Clinically stable, disease present  
 3=Disease has recurred/progressed but asymptomatic  
 4=Recurred/progressed and causing clinical signs/symptoms
- A. If "3" or "4" above, was recurrence/progression: (1=Local, 2=Regional, 3=Systemic) .....
8. Was patient hospitalized since last visit? (1=Yes, 2=No) .....   
 A. If Yes, was hospitalization related to CAP or CAP therapy? (1=Yes, 2=No) .....   
 (If Yes, complete Form 05, Summary of Treatment for CAP.)

CLINICAL STAGING INFORMATION

9. Clinical stage of disease ..... T =  N =  M =  R =

<u>T</u>	<u>N</u>	<u>M</u>	<u>R</u>
X	X	X	X
0	0	0	0
1a (A1)	1 (D1)	1a (D2)	1
1b (A2)	2 (D1)	1b (D2)	2
1c	3	1c (D2)	
2a (B1)			
2b (B2)			
3a (C1)			
3b (C1)			
3c (C1)			
4a (C2)			
4b (C2)			

10. Tumor size (digital rectal exam) .....   
 1=Not palpable  
 2=Palpable but tumor  $\leq$  1.5 cm in greatest dimension  
 3=> 1.5 cm in greatest dimension  
 4=Not stated/unknown

P.I.'s Signature \_\_\_\_\_

## CODES FOR VISIT NUMBERS

01 = 6 WEEKS  
02 = 3 MONTHS  
03 = 6 MONTHS  
04 = 9 MONTHS  
05 = 12 MONTHS  
06 = YEAR 2 - VISIT 1 (18 months)  
07 = YEAR 2 - VISIT 2 (24 months)  
08 = YEAR 3 - VISIT 1 (30 months)  
09 = YEAR 3 - VISIT 2 (36 months)  
10 = YEAR 4 - VISIT 1  
11 = YEAR 4 - VISIT 2  
12 = YEAR 5 - VISIT 1  
13 = YEAR 5 - VISIT 2  
14 = YEAR 6 - VISIT 1  
15 = YEAR 6 - VISIT 2  
16 = YEAR 7 - VISIT 1  
17 = YEAR 7 - VISIT 2  
18 = YEAR 8 - VISIT 1  
19 = YEAR 8 - VISIT 2  
20 = YEAR 9 - VISIT 1  
21 = YEAR 9 - VISIT 2  
22 = YEAR 10 - VISIT 1  
23 = YEAR 10 - VISIT 2  
24 = YEAR 11 - VISIT 1  
25 = YEAR 11 - VISIT 2  
26 = YEAR 12 - VISIT 1  
27 = YEAR 12 - VISIT 2  
28 = YEAR 13 - VISIT 1  
29 = YEAR 13 - VISIT 2  
30 = YEAR 14 - VISIT 1  
31 = YEAR 14 - VISIT 2  
32 = YEAR 15 - VISIT 1  
33 = YEAR 15 - VISIT 2  
99 = UNSCHEDULED VISIT

Patient Name \_\_\_\_\_ Patient No.    Medical Center No.

Medical Center Name \_\_\_\_\_ Date Completed Mo   Day   Yr

**INSTRUCTIONS: THIS FORM MUST BE COMPLETED EACH TIME A PATIENT UNDERGOES NEW TREATMENT FOR CAP. PATIENTS IN EXPECTANT MANAGEMENT GROUP SHOULD HAVE TREATMENT ONLY IF DISEASE IS SYMPTOMATIC OR METASTATIC. RADICAL PROSTATECTOMY OR RADIATION THERAPY IN EXPECTANT MANAGEMENT GROUP IS CONSIDERED PROTOCOL VIOLATION UNLESS UTILIZED FOR PALLIATION OF SYMPTOMS.**

**REASONS FOR TREATMENT FOR PROSTATE CANCER**

1=YES  
2=NO

Local Disease:

- 1. Persistent tumor despite prostatectomy .....
- 2. New mass on DRE/TRUS or other imaging study .....
- 3. Enlarging mass on DRE/TRUS or other imaging study .....
- 4. Hematuria due to CAP .....
- 5. Bladder outlet obstruction due to CAP .....

IF YES:

- A. AUA symptom score 20 .....
- B. Bothersome score  $\geq$  "a lot" .....
- C. Creatinine 2X baseline or  $\geq$  3.0 mg/dl .....

Regional Disease:

- 6. Persistent tumor despite prostatectomy .....
- 7. Ureteral obstruction with hydronephrosis .....
- A. If Yes, creatinine 2X baseline or  $\geq$  3.0 mg/dl .....
- 8. Pelvic pain .....
- 9. Lymph edema .....
- 10. Rectal obstruction .....

Metastatic Disease:

- 11. Positive bone scan .....
- 12. Positive roentgenograms .....
- 13. Increase in liver function tests and positive imaging study .....
- 14. Anemia .....
- 15. Reduction in functional status .....

1=YES  
2=NO

Abnormal Biomarkers:

- 16. Increasing or persistent PSA .....
- 17. Increasing prostatic acid phosphatase .....
- 18. Sexual Dysfunction .....
- 19. Incontinence .....
- 20. Other, specify \_\_\_\_\_ .....

**TYPE OF FOLLOW-UP INTERVENTION FOR PROSTATE CANCER SINCE LAST VISIT.**

1=YES  
2=NO

- 21. MECHANICAL .....
- A. If Yes, specify types:
- 1. TURP .....
- 2. TUIP .....
- 3. Stent (type) \_\_\_\_\_ .....
- 4. Other, specify \_\_\_\_\_ .....

1=YES  
2=NO

- 22. SURGERY .....
- A. If Yes, specify procedures:
- 1. Pelvic lymphadenectomy .....
- 2. Simple prostatectomy .....
- 3. Standard radical prostatectomy .....
- 4. Nerve sparing prostatectomy .....
- 5. Perineal prostatectomy .....
- 6. Other \_\_\_\_\_ .....
- 7. Unknown .....



23. RADIATION (1=Yes, 2=No) .....

IF YES:

A. Prostate (1=Yes, 2=No) .....

IF YES:

1. Type (1=External beam, 2=Interstitial, 3=Unknown) .....

2. Best response (1=CR, 2=PR, 3=Progressive DZ, 4=Unknown) .....

B. Pelvic lymph nodes (1=Yes, 2=No) .....

IF YES:

1. Type (1=External beam, 2=Interstitial, 3=Unknown) .....

2. Best response (1=CR, 2=PR, 3=Progressive DZ, 4=Unknown) .....

C. Parenchymal (1=Yes, 2=No) .....

IF YES:

1. Specify \_\_\_\_\_

2. Type (1=External beam, 2=Interstitial, 3=Unknown) .....

3. Best response (1=CR, 2=PR, 3=Progressive DZ, 4=Unknown) .....

D. Bone (1=Yes, 2=No) .....

IF YES:

1. Specify \_\_\_\_\_

2. Type (1=External beam, 2=Interstitial, 3=Unknown) .....

3. Best response (1=CR, 2=PR, 3=Progressive DZ, 4=Unknown) .....

24. BRACHY THERAPY (1=Yes, 2=No) .....

25. SYSTEMIC THERAPY SINCE LAST VISIT (1=Yes, 2=No) .....

IF YES:

Best Response  
 1 = CR  
 2 = PR  
 3 = Progressive DZ  
 4 = Unknown

<u>Type of Therapy</u>	<u>1 = Yes</u> <u>2 = No</u>	
A. Alpha Blockers .....	<input type="checkbox"/>	<input type="checkbox"/>
B. Chemotherapy .....	<input type="checkbox"/>	<input type="checkbox"/>
C. Immunotherapy .....	<input type="checkbox"/>	<input type="checkbox"/>
D. Orchiectomy .....	<input type="checkbox"/>	<input type="checkbox"/>
E. Adrenalectomy .....	<input type="checkbox"/>	<input type="checkbox"/>
F. Hypophysectomy .....	<input type="checkbox"/>	<input type="checkbox"/>
G. DES/estrogen .....	<input type="checkbox"/>	<input type="checkbox"/>
H. LHRH analog .....	<input type="checkbox"/>	<input type="checkbox"/>
I. Antiandrogens .....	<input type="checkbox"/>	<input type="checkbox"/>
J. Other hormone Rx .....	<input type="checkbox"/>	<input type="checkbox"/>
K. Other systemic _____ .....	<input type="checkbox"/>	<input type="checkbox"/>
<u>Sexual Dysfunction:</u>		
L. Penile injection .....	<input type="checkbox"/>	<input type="checkbox"/>
M. Prosthesis .....	<input type="checkbox"/>	<input type="checkbox"/>
N. Vacuum device .....	<input type="checkbox"/>	<input type="checkbox"/>
O. Other _____ .....	<input type="checkbox"/>	<input type="checkbox"/>
<u>Incontinence:</u>		
P. Teflon injections .....	<input type="checkbox"/>	<input type="checkbox"/>
Q. Artificial sphincters .....	<input type="checkbox"/>	<input type="checkbox"/>
R. Catheter device .....	<input type="checkbox"/>	<input type="checkbox"/>
S. Pads .....	<input type="checkbox"/>	<input type="checkbox"/>
T. Clamps .....	<input type="checkbox"/>	<input type="checkbox"/>
U. Other _____ .....	<input type="checkbox"/>	<input type="checkbox"/>

26. Did any of the above treatment involve unauthorized surgery, radiation, procedures, or other therapies on an expectant management patient? (1=Yes, 2=No) .....

P.I.'s Signature \_\_\_\_\_

Patient Name \_\_\_\_\_

Patient No.

Medical Center No.

Medical Center Name \_\_\_\_\_

Visit No.

Date Mo   Day   Yr

Answer every question by marking the appropriate box. If you are unsure about how to answer a question please give the best answer you can.

**A. SF-36™ HEALTH STATUS SURVEY**

1. In general, would you say your health is: *(circle one number)*

1	Excellent
2	Very Good
3	Good
4	Fair
5	Poor

2. Compared to one year ago, how would you rate your health in general now? *(circle one number)*

1	Much better now than 1 year ago
2	Somewhat better now than 1 year ago
3	About the same
4	Somewhat worse now than 1 year ago
5	Much worse now than 1 year ago

3. 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 one number 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 .....
- b. Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf .....
- c. Lifting or carrying groceries .....
- d. Climbing several flights of stairs .....
- e. Climbing one flight of stairs .....
- f. Bending, kneeling, or stooping .....
- g. Walking more than a mile .....
- h. Walking several blocks .....
- i. Walking one block .....
- j. Bathing or dressing yourself .....

	1	2	3
a.	1	2	3
b.	1	2	3
c.	1	2	3
d.	1	2	3
e.	1	2	3
f.	1	2	3
g.	1	2	3
h.	1	2	3
i.	1	2	3
j.	1	2	3

4. 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 physical health?  
(circle one number on each line)

- a. Cut down the amount of time you spent on work or other activities .....
- b. Accomplished less than you would like .....
- c. Were limited in the kind of work or other activities .....
- d. Had difficulty performing the work or other activities (for example, it took extra effort) .....

	YES	NO
a.	1	2
b.	1	2
c.	1	2
d.	1	2

5. 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 any emotional problems such as feeling depressed or anxious? (circle one number on each line)

- a. Cut down the amount of time you spent on work or other activities .....
- b. Accomplished less than you would like .....
- c. Didn't do work or other activities as carefully as usual .....

	YES	NO
a.	1	2
b.	1	2
c.	1	2

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

- 1 Not at all
- 2 Slightly
- 3 Moderately
- 4 Quite a bit
- 5 Extremely

7. How much bodily pain have you had during the past 4 weeks?  
(circle one number)

- 1 None
- 2 Very mild
- 3 Mild
- 4 Moderate
- 5 Severe
- 6 Very severe

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

- 1 Not at all
- 2 Slightly
- 3 Moderately
- 4 Quite a bit
- 5 Extremely

9. These questions are about how you feel and how things have been with you during the past 4 weeks. For each question, 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 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

10. 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.)? (circle one number)

1	All of the time
2	Most of the time
3	Some of the time
4	A little of the time
5	None of the time

11. 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	Not Sure	Mostly False	Definitely False
a. I seem to get sick a little easier than other people	1	2	3	4	5
b. I am as healthy as anybody 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

**B. AUA SYMPTOM INDEX**  
(circle one number on each line)

12. During the last month or so, how often have you had a sensation of not emptying your bladder completely after you finished urinating? .....

13. During the last month or so, how often have you had to urinate again less than 2 hours after you finished urinating? .....

14. During the last month or so, how often have you found you stopped and started again several times when you urinated? .....

15. During the last month or so, how often have you found it difficult to postpone urination? .....

16. During the last month or so, how often have you had a weak urinary stream? .....

17. During the last month or so, how often have you had to push or strain to begin urination? .....

	Not at All	Less Than 1 Time in 5	Less than Half the Time	About Half the Time	More than Half the Time	Almost Always
12.	0	1	2	3	4	5
13.	0	1	2	3	4	5
14.	0	1	2	3	4	5
15.	0	1	2	3	4	5
16.	0	1	2	3	4	5
17.	0	1	2	3	4	5

18. During the last month, how many times did you most typically get up to urinate from the time you went to bed at night until the time you got up in the morning? .....

	None	1 Time	2 Times	3 Times	4 Times	5 or More times
18.	0	1	2	3	4	5

**C. BOTHERSOME INDEX**

19. Overall, how bothersome has any trouble with urination been during the last month? (circle one number)

- |   |                       |
|---|-----------------------|
| 0 | Not at all bothersome |
| 1 | Bothers me a little   |
| 2 | Bothers me some       |
| 3 | Bothers me a lot      |

**D. PROSTATE SPECIFIC QUESTIONS**

URINE FLOW

20. In the past week did you:  
(circle one number)

1
2
3
4
5
6

- 1 Have total control 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 no control over your urine flow.
- 6 I have an indwelling catheter.

21. In the past week have you used any of the following to prevent or protect you from being incontinent?  
(circle one number on each line)

- a. Worn a pad in underwear .....
- b. A clamp .....
- c. A catheter device .....
- d. Injection therapy .....
- e. Used medications .....
- f. Limited activity in order to be near a bathroom .....

	YES	NO
a.	1	2
b.	1	2
c.	1	2
d.	1	2
e.	1	2
f.	1	2

ERECTION

22. Please choose the answer that best describes your sexual capabilities.  
(circle one number)

1
2
3
4

- 1 I am able to have a normal erection and intercourse.
- 2 I am able to have an erection that allows vaginal penetration but is weaker than normal.
- 3 I am able to have an erection that is of insufficient strength for vaginal penetration.
- 4 I am unable to have an erection.

23. Have you had any sexual activity or intercourse during the past month? (circle one number) .....

YES	NO
1	2

a. If no, did this bother you? (circle one number)

1
2
3
4
5

- 1 Not at all
- 2 Just a little
- 3 Some
- 4 Fair amount
- 5 A lot

If Yes to Question 23, please answer Questions 24, 25, and 26.

24. In the last month, I would rate my level of interest in sexual activities as: *(circle one number)*

Very High	High	Moderate	Low	Very Low
1	2	3	4	5

25. In the last month, I would rate my sexual functioning as: *(circle one number)*

Very Good	Good	Moderate	Poor	Very Poor
1	2	3	4	5

26. In the last month, I would rate my satisfaction with my sexual functioning as: *(circle one number)*

Very Satisfied	Satisfied	Moderately Satisfied	Not Very Satisfied	Not Satisfied At All
1	2	3	4	5

**OVERALL HEALTH**

27. Please score how you feel your life has been affected by the state of your health (any disease or treatment) during the past week. *(circle one number)*

Extremely Unpleasant	Unpleasant	Moderately Unpleasant	Slightly Unpleasant	Normal
1	2	3	4	5

*(Circle one number on each line)*

28. How much physical discomfort would you say you have because of anything related to your prostate cancer or the effects of its treatments?

A Lot	Some	Only a Little	None at All
1	2	3	4

29. How much do you worry about your health because of anything related to your prostate cancer or the effects of its treatments?

1	2	3	4
---	---	---	---

30. How much would you say your day-to-day activities are limited by anything related to your prostate cancer or the effects of its treatment?

1	2	3	4
---	---	---	---

31. Overall, how much would you say you are bothered by anything related to your prostate cancer or the effects of its treatment?

1	2	3	4
---	---	---	---

32. Overall, how would you describe the way you feel about how your treatment has worked out? *(circle one number)*

Delighted	Pleased	Mostly Satisfied	Mixed	Mostly Dissatisfied	Unhappy	Terrible
1	2	3	4	5	6	7

33. How would you rate the medical care you received for prostate cancer? *(circle one number)*

Excellent	Very Good	Good	Fair	Poor
1	2	3	4	5

P.I.'s Signature \_\_\_\_\_



Patient Name \_\_\_\_\_ Patient No.  Medical Center No.

Medical Center Name \_\_\_\_\_ Date of Termination Mo  Day  Yr

1. REASON FOR TERMINATION .....

- 1=Study concluded
- 2=Patient died (complete Death Report below)
- 3=Patient withdrew, location known (date last seen is date of termination)
- 4=Lost to follow-up, location unknown
- 5=Other

**DEATH REPORT** (attach copy of autopsy report, death certificate, or discharge summary if available.)

2. Date of death ..... Mo  Day  Yr

3. Was autopsy performed? (1=Yes, 2=No) .....

A. If Yes, did autopsy show evidence of CAP? (1=Yes, 2=No) .....

IF YES:

B. Was disease locally confined? (1=Yes, 2=No) .....

C. Was there pathologic evidence of metastatic CAP? (1=Yes, 2=No) .....

CAUSES OF DEATH (use codes below to respond to each item):

1=No; 2=Primary cause; 3=Contributory; 4=Possible; 5=Unknown

- 4. Prostate cancer .....
- 5. Cardiovascular .....
- 6. Cerebrovascular .....
- 7. Pulmonary .....
- 8. Infectious .....
- 9. Non-CAP cancer .....
- 10. Suicide .....
- 11. Accident .....
- 12. Other, specify \_\_\_\_\_ .....

IF QUESTION 4 IS CODED "2", "3", OR "4", COMPLETE THE FOLLOWING:

1=YES  
2=NO

- 11. Toxicity from CAP related treatment .....
- 12. Pre-operative evaluation for CAP surgery .....
- 13. Morbid event occurring within 30 days after surgery .....
- 14. Morbid event within 30 days after randomization to Expectant Management .....

P.I.'s Signature \_\_\_\_\_

Patient Name \_\_\_\_\_

Patient No.

Medical Center No.

Medical Center Name \_\_\_\_\_

Date Completed Mo

Day

Yr

1. DATE OF BIOPSY/FINE NEEDLE ASPIRATION .....

Mo

Day

Yr

2. HISTOLOGIC GRADE .....

- 1=Well differentiated
- 2=Moderately well differentiated
- 3=Poorly differentiated/Undifferentiated
- 9=Unknown

P.I.'s Signature \_\_\_\_\_

Patient Name \_\_\_\_\_ Patient No.  Medical Center No.

Medical Center Name \_\_\_\_\_ Date Completed Mo  Day  Yr

---

RECORD VISIT NUMBER .....

1. DATE OF BLOOD SAMPLE ..... Mo  Day  Yr

2. PSA (ng/ml) (Abbot) ..... .

3. PAP - Enzymatic Assay (ng/ml) ..... .

4. PAP - Immunoassay (ng/ml) ..... .

P.I.'s Signature \_\_\_\_\_



**APPENDIX G**  
**PARTICIPATION**



**PARTICIPATION**

Listed below are names of investigators who have expressed willingness to participate in CSP#407 as of July 6, 1993. Please note that this does not include many nonVA centers that will participate through the NCI Oncology Groups.

VA MEDICAL CENTERS		
ALBUQUERQUE, NM Dr. Powers	FORT HARRISON, MT Michael Agee	MILWAUKEE, WI Christopher Dixon
ANN ARBOR, MI Rodney Davis	FORT WAYNE, IN Christopher Steidle	OKLAHOMA CITY, OK William Parry
ASHEVILLE, NC Earl Shook	GAINESVILLE, FL Howard Epstein	PALO ALTO, CA John Kabalin
ATLANTA, GA Sam D. Graham	HAMPTON, VA Ali Farpour	PITTSBURGH, PA Raoul Salup
BAY PINES, FL Perry Hudson	HOUSTON, TX Dov Kadmon	PORTLAND, OR Thomas Klein
BIRMINGHAM, AL Donald A. Urban	INDIANAPOLIS, IN Richard Foster	PROVIDENCE, RI August Zabbo
BRONX, NY Vincent Ciavarra	IOWA CITY, IA Bernard Fallon	SAN ANTONIO, TX Thomas Ball
BROOKLYN, NY Arthur Crowley	KANSAS CITY, MO John D. Foret	SAN FRANCISCO, CA Perinchery Narayan
CASTLE POINT, NY Bok Lee	LEXINGTON, KY David P. Wood	SAN JUAN, PR Luis Baez Macso
CINCINNATI, OH Patrick O'Donnell	LITTLE ROCK, AR Michael J. Schutz	SEATTLE, WA William Ellis
CLARKSBURG, WV Unyime Nseyo	LOS ANGELES, CA Brent Trieger	SHREVEPORT, LA Dan Culkin
COLUMBIA, MO Steven Weinstein	MADISON, WI Timothy Moon	SYRACUSE, NY Dennis Krauss
DALLAS, TX Claus G. Roehrborn	MANHATTEN, NY Pablo L. Torre	TAMPA, FL
DENVER, CO E.D. Crawford	MEMPHIS, TN Al Patterson	TEMPLE, TX Charles F. Johnson
DURHAM, NC Phillip J. Walther	MIAMI, FL Mark Salloway Arnon Krongrad	WEST ROXBURY, MA Joseph Jacobson Subbarao Yalla
EAST ORANGE, NJ Mitchell Bamberger		WHITE RIVER JUNCTION, VT Thomas Davis

**PARTICIPATION (Cont.)**

<b>NONVA CENTERS</b>	
<p><b>ANN ARBOR, MI</b> (University of Michigan) Rodney Davis</p>	<p><b>LEXINGTON, KY</b> (University of Kentucky) David P. Wood</p>
<p><b>ATLANTA, GA</b> (Emory University) Sam D. Graham</p>	<p><b>LOS ANGELES, CA</b> (UCLA) Brent Trieger</p>
<p><b>BIRMINGHAM, AL</b> (University of Alabama) Donald A. Urban</p>	<p><b>MADISON, WI</b> (University of Wisconsin) Timothy Moon</p>
<p><b>BRONX, NY</b> Vincent Ciavarra</p>	<p><b>MEMPHIS, TN</b> (University of Tennessee) Al Patterson</p>
<p><b>BROOKLYN, NY</b> Arthur Crowley</p>	<p><b>MILWAUKEE, WI</b> (University of Wisconsin) Christopher Dixon</p>
<p><b>BURLINGTON, VT</b> (University of Vermont) John Roberts</p>	<p><b>PITTSBURGH, PA</b> (University of Pittsburgh) Raoul Salup</p>
<p><b>CLARKSBURG, WV</b> (University of West Virginia) Unyime Nseyo</p>	<p><b>OAKLAND, CA</b> (Oakland Naval Hospital) Raymond Leidich</p>
<p><b>DALLAS, TX</b> (University of Texas) Claus G. Roehrborn</p>	<p><b>SAN FRANCISCO, CA</b> (University of California/San Francisco) Perinchery Narayan</p>
<p><b>DURHAM, NC</b> (Duke University) Phillip J. Walther</p>	<p><b>SEATTLE, WA</b> (University of Washington) William Ellis</p>
<p><b>FORT SAM HOUSTON, TX</b> (Brooke Army Medical Center) Ian Thompson</p>	<p><b>SHREVEPORT, LA</b> (Louisiana State) Dan Culkin</p>
<p><b>GAINESVILLE, FL</b> (University of Florida) Howard Epstein</p>	<p><b>TRIPLER AMC, HI</b> (Tripler Army Medical Center) Steven Gange</p>
<p><b>HOUSTON, TX</b> (Baylor College of Medicine) Peter Scardino</p>	
<p><b>IOWA CITY, IA</b> (University of Iowa) Bernard Fallon</p>	



**PIVOT Protocol Refinements and Updates for A priori Analyses Some Which will be incorporated into the Initial PIVOT Manuscripts 11/5/10**

**Intended for Writing Group Purposes**

**Meeting Discussions: January 6<sup>th</sup> and 8<sup>th</sup>, 2010:**

**Writing Group Members: Wilt, Brawer, Barry, Aronson, Wei, Jones, Culkin, Wheeler**

**Manuscript #1: The Prostate cancer Intervention Versus Observation Trial (PIVOT): a VA/NCI/AHRQ Randomized Trial Comparing Radical Prostatectomy With Watchful Waiting In Men with Clinically Localized Prostate Cancer.**

**Main Analyses:**

**1) Main Outcomes: Primary: Overall Mortality:** Time to death from any cause; **Secondary: Prostate Cancer Specific Mortality:** Time to prostate cancer death Defined as Death Adjudicated by Endpoints Committee as: Definitely or Probably Due to Prostate Cancer or Definitely or Probably Due to Prostate Cancer Treatment

**a) Intention to treat (RP vs. WW as randomized) analysis**

- a. Time of analysis:
  - i. Time to event
  - ii. Prespecified intervals (30d, mean/median FU [approx 13 years], 5, 10)
  - iii. Time to intervention:
    1. RP: time to patients receiving RP (n/N, %, mean time, hazard curves)  
WW: time to patients receiving RP (n/N, %, mean time, hazard curves)  
Type of approach  
Type of procedure  
Reasons for breach of protocol
    2. RP Group: time to patients receiving any definitive therapy (RP, EBRT or Brachytherapy) (n/N, %, mean time)  
WW Group: pts receiving any definitive therapy (n/N, %, mean time)
- b. Subgroups: 4 major prespecified: Age, Race, PSA, Tumor characteristic)
  - i. Age: (< vs. >=65)
  - ii. Race: White, Black, Other
  - iii. PSA: < vs >= 10 ng/mL as determined by local laboratory:
    1. Central PSA Laboratory data will be utilized to assess disease progression outcomes
  - iv. Gleason Histology: 2-4, 5-6, 7, 8-10 or <7 vs. >=7
    1. The Histologic Grade and Clinical Stage used for all analyses will be that ascribed by the local site pathologists and investigators
  - v. Tumor stage: clinical stage as attributed at randomization visit
    1. In particular: T1C and Tumors detected by elevated PSA or change in PSA (Q4: Form 2)
  - vi. Tumor risk classification using clinical stage, PSA, Grade: low, medium high
  - vii. Above data as continuous and/or categorical variables in Cox hazards model
  - viii. Tests of interaction and effect modification between variables and outcomes
  - ix. Patient comorbidity scores; Charlson 0 vs. >=1 (Modified 10/10 in Perry Point); Performance Status: Form 02 Q5: (Response of 0-1) Fully active or Symptoms but ambulatory and able to do light work vs. Response of 2-4. Self reported

health status of: good, VG or Excellent vs: worse health status. Comorbidity classification revised 10/10 at Perry Point.

b) Sensitivity analyses:

i) Treatment received

- 1) RP Group: patients receiving RP
- 2) WW group: patients not receiving RP
- 3) RP Group: patients receiving any definitive therapy (RP, EBRT or Brachytherapy)
- 4) WW Group: patients not receiving any definitive therapy
- 5) Excluding randomized subjects without cancer at randomization by local pathology reading
- 6) Excluding randomized subjects without cancer at randomization as determined by central reading of submitted biopsy specimen
- 7) Analyses of mortality outcomes by histological grade and tumor risk classification according to central laboratory grading

ii) Excluding men where local or central biopsy specimen reading did not confirm cancer

- 1) Local biopsy specimen negative for cancer (regardless of central reading)
- 2) Central reading of submitted biopsy specimen was negative for cancer (regardless of local reading)

**2) Additional Secondary Outcomes (not QOL related):**

a. Disease Progression or recurrence:

Form 4:Q7 Stable (NEM); Stable (DZ); Disease; asym; DZ symp

i. Local

ii. Regional

iii. Metastatic: Note original protocol:

1. Additionally: + Bone scans coded 4 or 5 for KQ4 on Form 4. (Sensitivity secondary analyses will include adding those with coding of 3)

iv. CaP related hospitalizations Q8

b. PSA free survival /progression: (criteria remain to be finalized 11/10)

i. PSA free survival: Survival with PSA remaining < 0.04

ii. PSA recurrence following RP:

iii. Post RP PSA value of  $\geq 0.2$  with a subsequent confirmatory value  $\geq 0.2$  from the central laboratory (categorized as Yes/No and then time to recurrence...with the time to recurrence being the 2nd confirmatory report).

iv. PSA persistence following RP

1. PSA does not fall to < 0.04 at 6 months after RP

v. PSA progression

1. Following RP:

a. Definition to be clarified

b. Institution of hormonal or other therapy for PSA rise or elevation

2. In WW group:

a. PSA > 20 and at least 2x baseline:

b. Institution of hormonal or other therapy for PSA rise or elevation

c. Bony Metastases: + Bone scans: Baseline, Year 4, 8, 12 [Form 4: Code 4 or 5: Definitely malignant: axial skeleton; definitely malignant > 1 site]). Will also include Cod 3 if other supportive evidence of bony metastases.

- d. Additional Treatment
  - i. Mechanical
  - ii. Surgical
  - iii. Hormonal therapy (orchiectomy, LHRH, AA) ( n/N, %, time to use)
  - iv. Palliative radiation (n/N, % time to use)
  - v. Laminectomy (n/N, % time to use)
- e. Reasons for treatment
  - i. Local Disease
  - ii. Regional Disease
  - iii. Metastatic Disease
  - iv. Abnormal Biomarkers
- f. 30-day surgical complications in RP group by complication
- g. Surgical Histopathologic Parameters:
  - i. Confined to prostate
  - ii. Capsular invasion
  - iii. Capsular penetration
  - iv. Surgical margins involved
  - v. Seminal vesical invasion
  - vi. Metastatic Disease
  - vii. Unknown

**3) Tables and Figures (main manuscript):**

- a. Figure 1: CONSORT Study Flow Diagram
- b. Table 1: Base-Line Characteristics (see Baseline Paper)
- c. Table 2: Cause of Death
- d. Figure 2a: All-cause mortality; 2b: <65 vs. >=65
- e. Figure 3: Disease specific mortality
- f. Table 3: Cumulative incidence of Main Endpoints: 5 and 10 years
  - i. Overall mortality
  - ii. Disease Specific Mortality
  - iii. Distant Metastases;: Baseline, Year 1, 5, 10, end of study
  - iv. Local Progression
  - v. Use of Hormonal Therapy
  - vi. Additional palliative treatment: radiation, laminectomy, chemotherapy (individually and cumulatively)

# FILE

*PIVOT - Joe C  
letter  
(see stamp)*



DEPARTMENT OF VETERANS AFFAIRS  
MARYLAND HEALTH CARE SYSTEM (VAMHCS)  
Medical Center  
Perry Point, Maryland 21902

October 25, 1999

In Reply Refer To: 512A/151E  
CS#93/#407

John R. Feussner, M.D.  
Chief Research & Development Officer (125)  
Cooperative Studies Program  
VA National Headquarters (VACO)  
810 Vermont Avenue, N.W.  
Washington, D.C. 20420

*\$2,20 Mill previous  
current request \$1.35 Mill TOTAL  
\$850M*

Dear Dr. Faussner,

In response to our conversation at the Executive Committee meeting for CS#475, "Antibiotic Treatment of Gulf War Veterans' Illnesses." on October 13, 1999, I am rewriting our request for continued funding for CS#407 "Prostate Cancer Intervention Versus Observation Trial (PIVOT)." Based on the budget projection for a capitation system contained in my letter of October 5, 1999, we are requesting \$675,000 for each of the next two years to continue the recruitment of patients into this study until its currently scheduled end of recruitment date. Thus, we are requesting a total of \$1,350,000 for the next two years. In the currently approved budget, we had requested \$1,100,000 for each of the next two years. Therefore, this revised budget is a savings of \$850,000 over the next two years.

It should be kept in mind that this request is a maximum amount of funding. If recruitment is slower than expected over the next two years, then, since we are using capitation, there will be even greater savings. Once we know what our final recruitment figures are, we will be able to calculate more accurately the cost for continued follow-up for the eight year period where there is only follow-up and no recruitment. This eight year follow-up period should cost about \$300,000 per year.

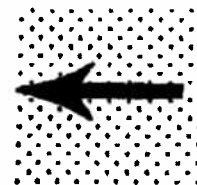
If you have any questions about this request, call me.

Sincerely,

*Joseph F Collins*  
JOSEPH F. COLLINS, Sc.D.  
Director, Cooperative Studies Program  
Coordinating Center

APPROVE / DISAPPROVE

*John R Feussner*  
JOHN R. FEUSSNER, M.D.





DEPARTMENT OF VETERANS AFFAIRS  
MARYLAND HEALTH CARE SYSTEM (VAMHCS)  
Medical Center  
Perry Point, Maryland 21902

October 5, 1999

In Reply Refer To: 512A/151E  
CS#93/#407

John R. Feussner, M.D.  
Chief Research & Development Officer (125)  
Cooperative Studies Program  
VA National Headquarters (VACO)  
810 Vermont Avenue, N.W.  
Washington, D.C. 20420

Dear Dr. Feussner,

In a May 28, 1999 memorandum to me and Dave Weiss, you had requested a contingency plan for the continuation of the PIVOT Trial (CSP#407), including justification of continued study recruitment, the feasibility of converting totally to a capitation model for funding, and statistical power estimates for the current sample size. After several months of writing and revising this plan, especially the budget, which was delayed by Dr. Weiss' illness, we have completed the plan which is attached.

As Dr. Wilt, the Study Chairman, discusses in his letter, the study question, watchful waiting versus radical prostatectomy for treatment of early stage prostate cancer, is still an important question to resolve. This has been made clear to me as I have been hearing various discussions at the recent SELECT study planning meetings. In addition, I believe that this is a study where the VA can make a significant contribution as NCI could not do such a study based on their recruitment into PIVOT and their previous failures in this type of study. Thus, I believe that it is very important to complete this trial even with just the current study patients.

As far as continuing patient recruitment, I also believe that it is important to continue recruiting. As seen in the sample size tables, with our current sample size (plus 24 patients), we would be able to detect a reasonable mortality difference (25%) with reasonable power (86%) with a 10 year follow-up period. The 10 year follow-up period would leave the study at its originally planned 15 year length. As the table indicates, with increased sample size, we will be able to detect smaller differences with about the same power and the same 15 year total length of the study. Since this is a study that most likely will never be repeated, I would argue to enter as many patients as possible in a specified time frame. That is, continue recruiting for the currently approved seven years and stop whether or not we achieve the 740 patients that Dr. Wilt is currently projecting. What I think makes such a plan feasible is the reverting back to a capitation system of funding. Thus, we would only be paying for what we get. If we achieve the full 740 patients that Dr. Wilt is projecting, then this will cost us about \$650,000 to \$700,000 for each of the next two years (including follow-up costs for already enrolled patients and the new patients). If we do not achieve the 740 patients, the costs will be lowered accordingly.

2.

October 5, 1999

John R. Feussner, M.D.

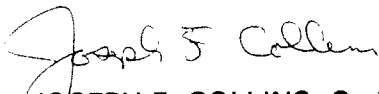
The capitation plan that Dr. Wilt is proposing would reduce the cost of the study significantly from FY98 levels where a mixture of secured funding and capitation was used. The reduction would be about \$400,000. In addition, this budget plan would bring the study costs for the recruitment phase back down to the levels originally proposed when the study was first approved. That original budget, however, was for significantly more patients. Given the extreme difficulty of randomizing the patients and the enormous amount of time required to discuss the study with potential subjects, the \$3,500 per randomization is probably fair and realistic compensation.

Finally, I would like to mention that Dr. Wilt has been an active member of the VA component in the SELECT study planning and has worked hard to connect the PIVOT and SELECT trials as much as possible. While it will not be mandatory that the PIVOT investigators participate in SELECT, it will be encouraged. It will be pointed out to the PIVOT investigators that compensation from the two studies will probably be sufficient for them to hire a full-time study coordinator during the recruitment phases of the two studies.

Based on the importance of the study and the ability of the VA to make an important and unique contribution to the treatment of prostate cancer, I would recommend continuation of the study. I would further recommend continuation of recruitment not to a fixed sample size but to a fixed date (seven years recruitment) based on the proposed capitation system.

If you have any questions about this response or require additional information, call me.

Sincerely,



JOSEPH F. COLLINS, Sc.D.  
Director, Cooperative Studies Program  
Coordinating Center

Enclosure

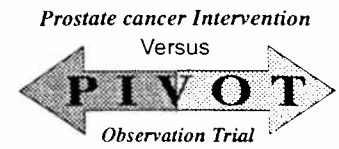
cc: Timothy Wilt, M.D.

APPROVE / DISAPPROVE

JOHN R. FEUSSNER, M.D.



**DEPARTMENT OF VETERANS AFFAIRS**  
**Medical Center**  
**PIVOT**  
**One Veterans Drive**  
**Minneapolis, MN 55417**



Date: September 21, 1999

From: Chairman, VA/NCI/AHCPR CSP #407:PIVOT  
 Re: CSP#407 Recruitment and Budget  
 To: Chief Research and Development Officer

In Reply Refer To: *VA/NCI Cooperative Study #407*

Timothy J. Wilt, MD, MPH, Co-Chair  
 Debra A. McKeehen, MS,  
 Project Coordinator

1. In response to a memo of May 28, 1999 I provide the following contingency plan.

Phone: (FTS) 8-700-780-4586  
 or (612) 725-2000 x 4586  
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 Mail Stop: **PIVOT**

**a. Justify continued study recruitment:**

PIVOT addresses the most important question in prostate cancer; does radical prostatectomy or expectant management provide superior length and quality of life in men with early prostate cancer? Health care organizations emphasize that this uncertainty will persist until PIVOT is completed. Because of the time and effort inherent to answering this question there will not be another opportunity to conduct this study. The enclosed revised capitated budget is a cost-efficient, incentive based strategy that represents a reduction of over 35% (\$400,000) from FY99. This budget will insure continued recruitment during the initial screening phase of the Selenium and Vitamin E Chemoprevention Trial [SELECT]. Initiation of wide-spread prostate cancer screening for SELECT will enhance identification of PIVOT eligible men. In turn, PIVOT sites already have partially funded coordinators who are dedicated to conducting prostate cancer trials. Combined funding from PIVOT and SELECT will provide added value to both studies, site investigators and the VA:CSP as each study will provide partial funding to support personnel necessary for successful recruitment.

PIVOT recruitment, while not at goal level, is unprecedented in its success. This achievement has been due almost entirely to the participation of veterans and VA investigators. PIVOT has demonstrated that VA is a leader in conducting scientifically important but feasibly difficult studies in prostate cancer. This has facilitated additional research partnerships between VA and NCI, AHCPR, and the American College of Surgeons.

Recruitment at current rates until the end of year 7 will allow enrollment of 740 men (current enrollment = 576). PIVOT will be the largest randomized trial of surgery versus expectant management for early stage prostate cancer. With a sample size of 740, PIVOT will have 91% power to detect a 25% reduction in mortality and 80% power to detect a 20% reduction in mortality assuming a median survival of 10 years and a cross-over rate of 20%. PIVOT will have > 95% power to detect small differences in quality of life and the combined end point of mortality or development of metastatic disease.

If recruitment is terminated January 2000 PIVOT will enroll 600 men. PIVOT would have a power of 86% to detect a 25% mortality reduction and might fail to detect a clinically important 20% difference in survival. The estimated total number of events and the difference in the number of events between treatment groups that will occur if enrollment is limited to 600 men is less (195/146) than with enrollment of 740 men (228/171). The confidence intervals around the estimates with 600 men will be wider. VA PIVOT would be smaller than a comparable Swedish trial (total n = 690; 9 years for enrollment).

Number enrollees	Mortality reduction (%)	Approximate Power (%)			
		Median Survival (10 years)			
		Follow-up (years)			
600 (5 year recruit)	20	68	70	72	74
	25	86	88	90	92
		8	9	10	11
740 (7 year recruit)	20	80	82	84	86
	25	91	93	95	97
Total study duration (years)		15	16	17	18

We have taken the following additional steps to increase recruitment in a cost-efficient fashion: developed a capitated/incentive based budget; created a PIVOT Web page; increased dissemination through the American Cancer Society; established collaboration with (SELECT); obtained funding from AHCPR to supplement centers' funding and establish valuable longitudinal cohort studies in PIVOT screenees.

**b. Capitated study model**

We have developed and enclosed a revised capitated budget (Table 1). This represents a reduction of over 35% (\$400,000) from the FY99 annual budget of \$1.1 million and is directly related to continued productivity. The budget assumes that 70 patients per year will be enrolled in years 6 and 7 (total sample size = 740). Because we estimate that no patients will die or be lost to follow-up the actual budget will be less than the enclosed proposal and would offset additional costs related to recruitment that exceeds our estimates. Comparable percentage budget reductions at the Albuquerque CSPCC laboratory and Perry Point CSPCC would provide additional cost savings.

The funding levels and incentives allocated for recruitment and follow-up reflect the uniquely intensive time and effort required for enrollment and retention in a cancer trial that is comparing surgery to expectant management. Funding to continue recruitment and completion of screening logs in years 6 and 7 is approximately \$380,000 annually above follow-up costs. These are relatively modest sums given the importance of, and long standing commitment to, PIVOT and rely on successful incentive techniques utilized in other cancer trials. The monthly screening logs provide a registry of all men with newly diagnosed prostate cancer. In combination with the previously described AHCPR funded proposal, this registry provides the most complete cohort of prostate cancer patients ever established in VA and will allow for evaluation of treatment preferences and outcomes.

The proposed resources are sufficient to support continued PIVOT recruitment and follow-up efforts because many PIVOT investigators are likely to participate in SELECT. Furthermore, SELECT recruitment will be facilitated by the existence of successful and enthusiastic investigators and coordinators at over 40 VA sites that are partially supported by PIVOT. This proposal is strongly endorsed by the SELECT planning committee and PIVOT investigators.

Relying solely on SELECT funding would not provide adequate resources or incentive for PIVOT recruitment. The mass screening strategy utilized for SELECT is vastly different from the individual intensive efforts required for PIVOT recruitment. The SELECT cohort study, while complementing PIVOT and its screenee cohort will address multiple health issues that are not related to prostate cancer.

**c. Statistical power estimates with prolonged follow-up**

If enrollment of VA PIVOT is ended at 5 years with 600 men and follow-up extended for a total study duration of 17 years the power to detect a 25% reduction in mortality would increase from 86% to 90%. This is feasible but less desirable than our proposed plan with enrollment of 740:

- enrollment of 740 men will provide greater power to detect smaller survival differences
- PIVOT will be the largest and most clinically relevant trial on early prostate cancer treatment if enrollment exceeds 700
- the sample size calculations shown in the table above indicate that if event rates are less than expected, prolonged follow-up with 740 men will provide much greater power compared to ending enrollment at 600 men
- the costs of a 15 year study involving 740 patients is comparable to a 17 year study of 600 patients

2. While recruitment to PIVOT is difficult it is successful. This success is highlighted by the interest of NCI in collaborating with VA on the design and conduct of SELECT. The capitated budget including leveraged funding with AHCPR and partnership with SELECT will insure that continued recruitment is feasible, can be accomplished in a cost-efficient fashion and will assist with SELECT accrual. Power estimates indicate that PIVOT will be able to provide definitive answers to the most clinically important questions in early prostate cancer and that VA will continue to be a leader in the successful conduct of surgical cancer trials.

3. PIVOT investigators and I look forward to completing PIVOT and collaborating on SELECT.



TIMOTHY J. WILT, MD, MPH  
Chairman, VA/NCI/AHCPR CSP#407 PIVOT



**PIVOT (CSP#407) REVISED BUDGET 8/31/99**

Site #	VAMC	Enrolled 8/1/99	Screening log \$200 x 12	Randomization \$3500 x 2 pt./yr.	FU \$500/ pt. /yr.	Total/ Site	
500	Albany	19	\$2,400	\$7,000	\$9,500	\$18,900	
504	Amarillo	14	\$2,400	\$7,000	\$7,000	\$16,400	
506	Ann Arbor	11	\$2,400	\$7,000	\$5,500	\$14,900	
509	Augusta	0	\$2,400	\$7,000	\$0	\$9,400	
521	Birmingham	18	\$2,400	\$7,000	\$9,000	\$18,400	
531	Boise	10	\$2,400	\$7,000	\$5,000	\$14,400	
526	Bronx	9	\$0	\$0	\$4,500	\$4,500	
527	Brooklyn	25	\$2,400	\$7,000	\$12,500	\$21,900	
528	Buffalo	19	\$2,400	\$7,000	\$9,500	\$18,900	
537	Westside Chicago	8	\$2,400	\$7,000	\$4,000	\$13,400	
540	Clarksburg	32	\$2,400	\$7,000	\$16,000	\$25,400	
549	Dallas	23	\$2,400	\$7,000	\$11,500	\$20,900	
552	Dayton	0	\$2,400	\$7,000	\$0	\$9,400	
561	East Orange	16	\$2,400	\$7,000	\$8,000	\$17,400	
569	Fort Wayne	18	\$2,400	\$7,000	\$9,000	\$18,400	
590	Hampton	39	\$2,400	\$7,000	\$19,500	\$28,900	
580	Houston	4	\$2,400	\$7,000	\$2,000	\$11,400	
583	Indianapolis	7	\$2,400	\$7,000	\$3,500	\$12,900	
584	Iowa City	10	\$2,400	\$7,000	\$5,000	\$14,400	
596	Lexington	6	\$2,400	\$7,000	\$3,000	\$12,400	
598	Little Rock	17	\$2,400	\$7,000	\$8,500	\$17,900	
600	Long Beach	25	\$2,400	\$7,000	\$12,500	\$21,900	
691	Los Angeles	11	\$2,400	\$7,000	\$5,500	\$14,900	
607	Madison	2	\$0	\$0	\$1,200	\$1,200	
614	Memphis	12	\$2,400	\$7,000	\$6,000	\$15,400	
626	Nashville	0	\$2,400	\$7,000	\$0	\$9,400	
635	Oklahoma City	2	\$0	\$0	\$1,000	\$1,000	
640	Palo Alto	2	\$2,400	\$7,000	\$1,000	\$10,400	
646	Pittsburgh	12	\$2,400	\$7,000	\$6,000	\$15,400	
648	Portland	12	\$2,400	\$7,000	\$6,000	\$15,400	
650	Providence	11	\$2,400	\$7,000	\$5,500	\$14,900	
662	San Francisco	18	\$2,400	\$7,000	\$9,000	\$18,400	
663	Seattle	16	\$2,400	\$7,000	\$8,000	\$17,400	
665	Sepulveda	12	\$2,400	\$7,000	\$6,000	\$15,400	
667	Shreveport	12	\$2,400	\$7,000	\$6,000	\$15,400	
670	Syracuse	23	\$2,400	\$7,000	\$11,500	\$20,900	
673	Tampa	14	\$2,400	\$7,000	\$7,000	\$16,400	
674	Temple	36	\$2,400	\$7,000	\$18,000	\$27,400	
525	West Roxbury	1	\$0	\$0	\$500	\$500	
<b>TOTALS</b>			<b>\$84,000</b>	<b>\$245,000</b>	<b>\$263,200</b>	<b>\$592,200</b>	<b>\$592,000</b>

Additional incentives to sites:

Recruitment of 4 pts/yr.	\$5,000 x 6 sites x \$5,000	\$30,000
Recruitment of 8 pts/yr.	\$10,000 x 2 sites x 10,000	\$20,000
Recruitment of 12 pts/yr.	\$15,000 x 1 site X \$15,000	\$15,000
	<b>ESTIMATED TOTAL INCENTIVES</b>	<b>\$65,000</b>

**\$657,000**